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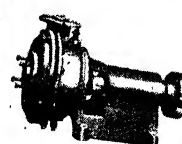
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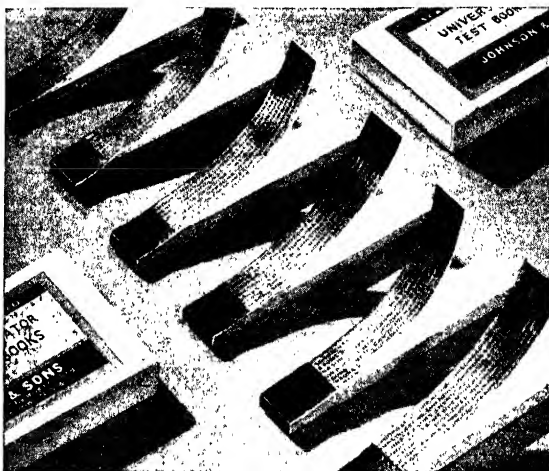
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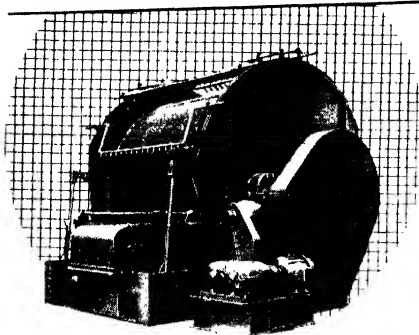
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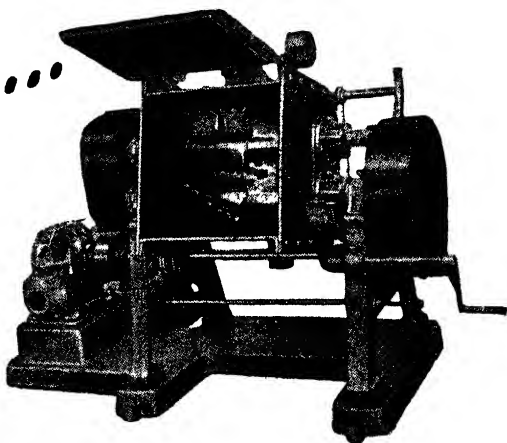
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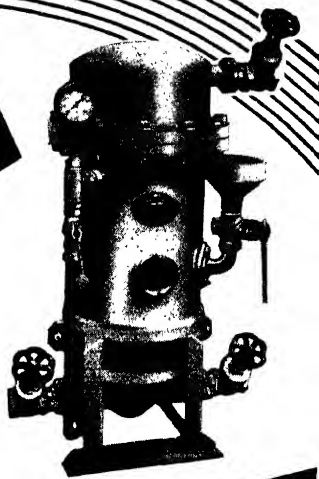
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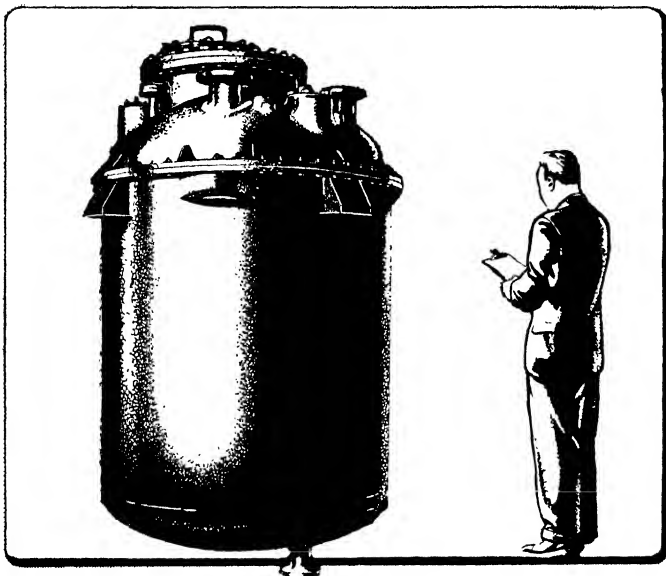
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CONTENTS.

| | PAGE |
|---|------|
| GENERAL AND PHYSICAL CHEMISTRY : | |
| 1. CHEMICAL REACTIONS INDUCED BY IONISING RADIATIONS. By F. S. DAINTON | 5 |
| 2. STRUCTURE OF AQUEOUS SOLUTIONS OF SOAP-LIKE SUBSTANCES. By G. S. HARTLEY | 33 |
| 3. CHEMICAL KINETICS: HOMOGENEOUS THERMAL GAS REACTIONS. By GWYN WILLIAMS and K. SINGER | 51 |
| INORGANIC CHEMISTRY : By R. E. DODD and P. L. ROBINSON . | 82 |
| ORGANIC CHEMISTRY : | |
| 1. INTRODUCTION. By D. H. HEY and BRYNMOR JONES | 118 |
| 2. GENERAL METHODS. By B. C. SAUNDERS | 122 |
| 3. HOMOLYTIC REACTIONS. By D. H. HEY | 139 |
| 4. TERPENES. By S. H. HARPER | 162 |
| 5. COLCHICINE AND RELATED COMPOUNDS. By J. D. LOUDON | 187 |
| 6. RECENT WORK ON THE REACTIONS OF ORGANIC SULPHUR COMPOUNDS. By J. F. W. MCMURIE | 198 |
| 7. HETEROCYCLIC COMPOUNDS. By J. A. ELVIDGE | 216 |
| BIOCHEMISTRY : | |
| 1. INTRODUCTION. By C. RIMINGTON | 238 |
| 2. THE FUNCTION OF SMALL MOLECULES IN BIOSYNTHESIS. By R. BENTLEY | 239 |
| 3. PARTITION CHROMATOGRAPHY. By A. J. P. MARTIN | 267 |
| 4. THE CHEMISTRY OF INSULIN. By F. SANGER | 283 |
| 5. THE CHEMOTHERAPEUTIC APPROACHES TO THE T.B. PROBLEM. By G. BROWNLEE | 292 |
| ANALYTICAL CHEMISTRY : | |
| 1. INTRODUCTION. By H. IRVING | 316 |
| 2. ANALYTICAL EMISSION SPECTROGRAPHY. By H. R. CLAYTON | 316 |
| 3. FLAME PHOTOMETRY. By L. LEYTON | 326 |
| 4. VOLUMETRIC ANALYSIS. By H. IRVING | 330 |
| 5. ANALYSIS OF SEA WATER. By H. BARNES | 338 |

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VOL. 44, 1947.

| Page | Line | |
|------|------|---|
| 65 | 16 | for 110.1 read 101.1. |
| 103 | 15 * | for $R_1 \cdot CCl_2 \cdot R_2$ read $R_1 \cdot CCl_2 \cdot R_2$. |
| 114 | 5 * | for 1935 read 1933. |
| 149 | 4 * | reference 33, after 33 insert Y. R. Naves, A. V. Gram-polloff, and P. Backmann. |
| 196 | 2 * | for $-CH_2 \cdot OH$ read $-CH_2 \cdot CHO$. |

* From bottom of page.

ANNUAL REPORTS ON THE PROGRESS OF CHEMISTRY.

GENERAL AND PHYSICAL CHEMISTRY.

1. CHEMICAL REACTIONS INDUCED BY IONISING RADIATIONS.

1. Chemical changes produced in a photographic emulsion by the absorption of rays emitted by a compound of uranium were the means of Becquerel's discovery of radioactivity in 1896¹ and are still used as a tool in modern research in nuclear physics.² Chemical changes brought about in living cells by X-rays are closely connected with the ensuing biological effects, and are therefore of great importance in the study of radiotherapeutics.^{3, 4} It is the more surprising, therefore, that the mechanism of radiochemical reactions has until recently been so imperfectly understood. The reason for this is that the most obvious result of the absorption of radiations from radioactive substances is the formation of ions, and, for about forty years after Becquerel's discovery, it was customary to ascribe all the chemical effects solely to the ion-pairs initially formed. The recognition of atoms and radicals in electrical discharges, and the growing realisation of the fact that molecular fragments are often much more reactive chemically when they are uncharged than when they are charged, have caused a considerable reorientation of views about the way in which radiochemical reactions proceed. A coherent account of this subject is therefore timely.

For the purpose of this Report, the subject of "*Radiation Chemistry*" will be defined as the study of the chemical effects produced by absorption of all types of rays emitted in radioactive transformations, of quanta of magnitude greater than about 50 ev., and of electrons or positive ions of this energy range. Ions are formed in all these instances, but we exclude all photochemical changes (from which radiochemical changes differ, see below) even when these latter occasionally lead to ionisation.⁵ Purely physical effects, such as radioluminescence, will not be discussed.

Several monographs which deal particularly with earlier investigations

¹ See J. Becquerel, "La Radioactivité," Chapt. I, Paris, 1924.

² See, e.g., F. C. Powell *et al.*, *Nature*, 1949, **163**, 47.

³ B. M. Dugger, "Biological Effects of Radiation," New York, 1936.

⁴ D. E. Lea, "Actions of Radiations on Living Cells," Cambridge, 1946.

⁵ E.g., G. Volmer and K. Riggert, *Z. physikal. Chem.*, 1922, **100**, 502.

from the purely ionic point of view have been published,⁶⁻¹¹ and the recent change of outlook is most clearly seen in the proceedings of two recent symposia,^{12, 13} and in the second chapter of the late Dr. D. E. Lea's book.⁴

2. Experimental Methods.—Reactions in discharges of all types have been fully discussed by G. Glockler and S. C. Lind.⁷ With the exception of the so-called "gas electrode"²¹ all such reactions are restricted to gases, often at low pressures in either static or flowing systems.

2 (i). Radiation sources. The radiation may be supplied from a source situated either inside or outside the reaction vessel. The use of external sources, which include all high-voltage machines, is a determining factor for the shape and material of the reaction vessel. Internal sources would minimise this restriction, but there are very few cases of their employment. A possible reason for this is the former scarcity of radioactive sources which emit substantially one type of radiation. For example, radium, though available, can be used as a γ -ray source only when the α - and β -rays are absorbed in a screening material and can never serve as a *pure* α -ray source.

(a) The principal *positively* charged rays are beams of helium nuclei, protons, and deuterons, all of which can be obtained from particle-accelerating machines such as the cyclotron and van der Graaff generator, and already some radiochemical studies have been made by this means.^{14, 15} Usually, natural radio-elements have been employed, *e.g.*, (a) polonium, which emits only α -rays of 5.3 Me.v. energy,¹⁶ (b) radon and its decay products, Ra-A and Ra-C' mixed with the reactants.^{17, 18} It is important to use the source in such a form that it is not a chemical catalyst for the destruction of the products.¹⁹ Other positive ions have occasionally been used, for instance, I. Moteschan *et al.*²⁰ have used singly-charged alkali-

⁶ S. C. Lind, "The Chemical Effects of Alpha Particles and Electrons," Chem. Catalog Co., Inc., 1928.

⁷ "The Electrochemistry of Gases and other Dielectrics," London, 1939.

⁸ Lind, *Chem. Reviews*, 1930, **7**, 203.

⁹ W. Mnd, "L'action chimique des rayons Alpha en phase gazeuse," Hermann et Cie., Paris, 1935.

¹⁰ A. Kailan, "Über die chemische Wirkung der durchdringenden Radiumstrahlung," Vienna, 1938.

¹¹ F. Wegmüller, "Wirkung der Roentgenstrahlen auf einige organische Verbindungen," Schüler, 1942.

¹² Symposium on "Radiation Chemistry and Photochemistry," University of Notre Dame, June 24th—27th, 1947; *J. Phys. Colloid. Chem.*, 1948, **52**, 437.

¹³ Second Session of the Conference on "Certain Aspects of the Action of Radiation on Living Cells," London, May 13th—14th, 1946; *Brit. J. Radiol.*, 1948 Suppl. No. 1, 41.

¹⁴ I. A. Breger, *J. Phys. Colloid. Chem.*, 1948, **52**, 551.

¹⁵ C. W. Sheppard and R. E. Honig, *J. Physical Chem.*, 1946, **50**, 144; C. W. Sheppard and V. L. Burton, *J. Amer. Chem. Soc.*, 1946, **68**, 1636.

¹⁶ H. Folmer, *Proc. K. Akad. Wetensch. Amsterdam*, 1932, **35**, 636.

¹⁷ P. C. Capron, *Ann. Soc. sci. Brux.*, B, 1935, **55**, 222.

¹⁸ L. H. Gray and J. Read, *Brit. J. Radiol.*, 1942, **16**, 125; 1941, **15**, 320.

¹⁹ *E.g.*, P. Bonet-Maury and M. Lefort, *Compt. rend.*, 1948, **226**, 1445.

²⁰ I. Moteschan, S. Roginsky, A. Schechter, and P. Theodorof, *Acta Physicochim. U.R.S.S.*, 1936, **4**, 757.

metal cations to induce the ammonia synthesis, and some of the changes obtained in aqueous solutions by V. I. Pavlov,²¹ using the so-called " gas-phase anode " method, are to be attributed to penetration of the solution by positive gas ions of energy $\sim 10^3$ ev. A novel recent development, which may prove valuable, is to use an external source of slow neutrons to irradiate a medium which can yield the required positive ions by a nuclear reaction. In this way, the advantage of an internal source would be combined with that of the easier control of dosage which is associated with external sources. The method has been applied to tissue,²² but the only chemical reaction initiated in this way is the polymerisation of styrene by recoil protons and bromine ions formed by the Szilard-Chalmers reaction.²³

(b) Fast anions have rarely been used, the most important *negatively* charged rays being electrons in the form of cathode or β -rays. Whenever external sources are used, the material to be irradiated should be in the form of thin layers, and, when a wall of a containing vessel has to be interposed between the source and the target, it should be as thin as is compatible with the mechanical strain which it will be required to bear. If the source is a radioactive element which is also α -active, the thickness of the wall must, of course, exceed the range of the highest-energy α -particle emitted. A common external β -ray source comprises radon " seeds," *i.e.*, thin-walled glass tubes containing radon gas, largely converted into an active deposit of Ra-B and Ra-C.²⁴ Many reinforced windows^{25, 26} made of thin glass, aluminium, or mica, backed by fine wire meshes, have been designed for use with accelerating machines which operate at low pressures, *e.g.*, discharge tubes, van der Graaff generators. The choice of a window material will, of course, be partly determined by the nature of the chemical reaction to be investigated.

Internal β -ray sources do not appear to have been used—a fact which is probably due to the lack of suitable naturally-occurring, purely β -emitting radio-elements, *e.g.*, meso-Th-2, in adequate quantities. Increased availability of artificial radio-elements such as ³²P, ⁹⁰Y, and ²⁰⁴Tl may remedy this deficiency.

(c) High-energy *photons*, *i.e.*, X- and γ -rays, possess a high penetrating power, which is an advantage in that large samples can be adequately irradiated even when external sources are used. Disadvantages are (i) that so much of the energy output of the source is wasted, and (ii) that considerable screening is required for the protection of personnel. All the work on γ -ray-induced reactions has hitherto been effected by radium,

²¹ *Compt. rend. Acad. Sci. U.R.S.S.*, 1944, **43**, 236, 383, 385.

²² P. A. Zahl and F. S. Cooper, *Radiology*, 1941, **37**, 673.

²³ I. Landler and M. Magat, *Compt. rend.*, 1948, **226**, 1720.

²⁴ A. T. Cameron and (Sir) Wm. Ramsay, *J.*, 1907, **831**, 1593; 1908, **966**, 992. For a modern method of preparing radon " seeds " see Spicer, *J. Sci. Instr.*, 1946, **23**, 207.

²⁵ See Chapter IV of ref. 7.

²⁶ W. D. Coolidge, *J. Franklin Inst.*, 1926, **202**, 693; C. M. Slack, *J. Opt. Soc. Amer.*, 1929, **18**, 123.

in equilibrium with its decay products, and in a container of wall thickness sufficient to filter out all α - and β -rays. The radiation thus emitted is not monochromatic, but consists of eight lines varying in energy from 0.189 to 2.198 Me.v. In contrast with the case of visible and ultra-violet radiation, the use of combinations of filters cannot lead to monochromatism; it merely excludes much radiation of the longer wave-lengths. For maximum utilisation of the γ -rays, the system to be studied is usually contained in a chamber which has a central cavity for the source.^{27, 28} Other γ -ray sources of high energy and long life could be used, *e.g.*, C'' , ^{24}Na , Y , ^{124}Sb , Mn , ^{85}Sr , and Co .

X-Rays are formed as scattered radiation when fast electrons fall on a prepared target, and consequently all machines which give electron beams can easily be converted for use as X-ray sources. The X-ray beam contains quanta of all energies from very low values almost to the acceleration voltage of the electrons, and becomes self-collimated more and more in the forward direction as this voltage is increased above 500 kv. In all X-ray experiments reported hitherto, the source has been either specially constructed or one of the convenient industrial units designed for radiography or deep therapy.^{27, 28}

(d) *Neutrons* also bring about ionisation in the material in which they are absorbed and have been used to initiate polymerisation.²⁹ The highest neutron fluxes are most readily available as pile radiation, but this also contains a large proportion of γ -rays.³⁰ Alternatively, *d,n* reactions could be employed.³¹

2 (ii). Reaction vessels and temperature control. With internal sources of particulate radiation (α , β , etc.) the reaction vessel can be of any shape and the reaction temperature controlled in the usual way by liquid or vapour thermostats. External sources require the use of very thin, but mechanically strong, windows [see 2 (i) (b)], and, since the range of such particles in dense media is very short,* it is preferable to use only thin films of material to be irradiated. Such a reaction vessel cannot be totally immersed in a thermostat and furthermore, a good deal of heating of the specimen and the adjacent window will occur. Reaction vessels for X- and γ -ray work can be of much larger dimensions, and normal methods of temperature control are possible.

2 (iii). Dosimetry. In order to measure the efficiency of the radiation in bringing about chemical reactions, it is essential to find the rate of energy absorption in the medium. Convenient units are electron-volts (ev.) per

²⁷ F. S. Dainton, *J. Phys. Colloid. Chem.*, 1948, **52**, 490.

²⁸ N. Miller, *Nature*, 1948, **162**, 448.

²⁹ F. L. Hopwood and J. T. Phillips, *ibid.*, 1939, **143**, 640.

³⁰ A. O. Allen, *J. Phys. Colloid. Chem.*, 1948, **52**, 479.

³¹ Ref. 4, p. 20.

³² R. K. Appleyard, private communication.

* *E.g.*, the range of the α -particle from Po (5.3 Me.v.) is 3.84 cm. in dry air at 15° and 760 mm., but probably only about 3.42×10^{-3} cm. in water.³²

litre per second. For internal sources of particulate radiation in reaction vessels which are large compared with the range of the particle, this "dose rate" is readily calculable from the concentration, half-life, and α - or β -ray energy of the radio-element employed.³³ When the range is long, as is the case in gas reactions, the calculation is more tedious.³⁴ When external beams of positive ions or electrons are used and all the rays reaching the reaction chamber are absorbed therein, the energy input can be estimated from the beam current, the energy of the ions, and the stopping power of the windows.

X- and γ -Ray dosimetry is less certain. Although the absorption of monochromatic X- or γ -ray photons is exponential with a coefficient characteristic of the energy of the photon and the absorbing substance, such coefficients are not readily determined. The reason for this lies in the fact that the energy is dissipated in the medium by photo-electrons and Compton recoil electrons [see section 3 (i) below]. In the latter mechanism, there is therefore a good deal of scattered radiation, only a proportion of which may be absorbed. Nevertheless, it is possible³⁵ to calculate the ratio of the absorption coefficients of any two media for a given wave-length, provided that their chemical compositions are known.

In practice, most estimates of the dose rate are based on measurements of the amount of ionisation produced either in the reacting system itself, if this is gaseous, or in an air-filled ionisation chamber. The method is limited by the difficulty of obtaining saturation currents in certain media. It is known that the mean energy dissipated in air at N.T.P. by electrons in creating an ion pair is 32.5 ev.³⁶ and hence the rate of ionisation gives a measure of the number of ergs absorbed. It is customary to define that quantity of radiation absorbed by 1 c.c. of dry air at N.T.P. which produces 1 E.S.U. of charge (2.1×10^9 ion pairs) as 1 roentgen; 1 c.c. of any other medium placed in the same position relative to the same source would absorb more energy, in the ratio of its volume absorption coefficients relative to that of air. The relative number of ion pairs formed will also be in this ratio if the same energy is required to create the ion pairs in the two media. In practice, the use of air-filled ionisation chambers in γ -ray dosimetry is not a simple problem, because almost all the ions formed in the small air cavity of the chamber are produced by the secondary electrons ejected from the walls of the chamber by the quanta which are absorbed or scattered therein. The implications of this for accurate dosimetry of aqueous solutions have been discussed by L. H. Gray³⁶ and N. Miller.³⁷

In principle, some of the difficulties of dosimetry could be avoided by using a reaction which is easily measured and the amount of which bears a

³³ *E.g.*, G. Glockler and G. B. Heisig, *J. Physical Chem.*, 1932, **36**, 769.

³⁴ *E.g.*, G. Glockler and R. Livingston, *ibid.*, 1934, **38**, 655.

³⁵ *Ref.* 4, p. 345.

³⁶ *Brit. J. Radiol.*, 1937, **10**, 600, 721; *Proc. Roy. Soc.*, 1936, *A*, **156**, 578.

³⁷ *In the press.*

fixed relation to the dose, as an integral dosimeter. Several attempts to construct such dosimeters have been made.³⁷⁻⁴⁰

3. The General Features of the Primary Radiochemical Act.—It is unlikely that any radiochemical reaction proceeds in one act, in the sense that the immediate consequence of absorption of some of the energy of the incident radiation is the conversion of the absorbing reactant molecule into the product. It is therefore convenient,⁴¹ as in photochemical processes, to divide the reaction into two stages: the primary act of energy absorption, and the secondary reactions which terminate in product formation. In accordance with U.S. practice the symbol $\sim\sim\sim\rightarrow$ will be used for the primary process.

3 (i). The mechanism of energy absorption. Positively charged ions passing through matter lose most of their energy by elastic impacts with electrons lying in their path. The gross disparity in mass of the colliding species means that the ion loses little velocity and is virtually undeflected, whilst the electrons may be ejected from the atoms to which they are bound, frequently with sufficiently high velocities to ionise other molecules.* Ion-pairs are thus formed along, or near, the track of the positively charged ions. Measurement of the total number of ion pairs per track and also of the number formed per element of length of the track (the specific ionisation) has established that (a) with α -rays, approximately 60% of the total number of ions formed are due to the secondary electrons, (b) the mean energy dissipated in a system per ion pair formed is about 30 ev., being independent of the velocity of the α -particle, but characteristic of the absorbing system, and (c) the specific ionisation is an inverse function of the velocity and roughly proportional to the square root of the atomic weight of the substance being ionised, when this substance is at some standard concentration. The theory of this process⁴² has been developed along classical lines by N. Bohr⁴³ and quantum-mechanically by H. Bethe⁴⁴ and F. Bloch.⁴⁵ Unfortunately, no accurate numerical predictions can be made from these theories. Thus, that of Bethe requires knowledge of an "average excitation potential," which is difficult to obtain *a priori* and which is usually evaluated empirically. Moreover, the treatment is restricted to atoms,

³⁶ H. Fricke and S. Morse, *Phil. Mag.*, 1929, **7**, 129.

³⁹ W. Stonstrom and H. R. Street, *Proc. Soc. Exp. Biol. Med.*, 1935, **32**, 1498.

⁴⁰ R. W. G. Wyckoff and L. E. Baker, *Amer. J. Roentgenol.*, 1929, **22**, 551.

⁴¹ F. S. Dainton, Report C.R.C. 304 (1946), not classified. N.R.C. (Canada), Division of Atomic Energy. Also M. Burton, ref. 12, p. 568, and J. O. Hirschfelder, ref. 12, p. 447.

⁴² For a general account of the physics of this process see F. Rosetti, "Elements of Nuclear Physics," London, 1937, and H. Bethe and M. S. Livingston, *Rev. Mod. Physics*, 1937, **9**, 246.

⁴³ *Phil. Mag.*, 1913, **25**, 10.

⁴⁴ H. Bethe, *Handbuch der Physik*, 1933, **24** (i), 519.

⁴⁵ *Z. Physik*, 1933, **81**, 363; *Ann. Physik*, 1933, **16**, 285.

* When the ejected electron has a very high velocity, say 1000 ev., it is known as a δ -ray. The tracks of such rays may be seen as spurs on α -particle tracks in the cloud chamber.

and hence the empirical Bragg additive law⁴⁶ must be used for problems involving molecules.

Electrons are of such low mass that, except when they possess extremely high energies, they are frequently deflected. The associated tracks have ill-defined ranges and are curved, particularly at low velocities. The experimental results and the theory⁴⁴ concerning the specific ionisation are very similar to the α -ray case discussed above. The specific ionisation is inversely proportional to the square of the velocity at low velocities, and less dependent at higher velocities, passing through a shallow minimum before increasing slowly at energies $>\sim 1$ Me.v. At low electron speeds, the specific ionisation is proportional to the atomic number of the absorbing material, but, due to the fact that the average excitation potential is also proportional to the atomic number, this proportionality does not hold amongst the higher elements. In addition to the energy lost by elastic impact, a small proportion, which increases with the electron energy, is lost by radiation as the electron is decelerated in passing through the field of the nucleus. This appears as a continuous X-ray spectrum (Bremstrahlung), and loss of energy due to this cause may assume serious proportions at electron energies in excess of 1 Me.v., especially for systems containing elements of high atomic number.

Whereas charged particles undergo a stepwise loss of energy, photons are absorbed in a single elementary act and hence a beam of X- or γ -rays of intensity I_0 will have fallen exponentially to a value $I_0 \cdot e^{-\epsilon d}$ at a distance d , where ϵ is an extinction coefficient characteristic of the wave-length and the absorbing medium. A high-energy photon may be absorbed by one of three mechanisms,* each of which will make its contribution to the total value of ϵ . The first mechanism which is especially prominent for soft radiation and absorbing media of high atomic number, is that of ejection of a photo-electron, which will have an energy equal to the magnitude of the quantum less the binding energy. Since the electrons most usually involved are those in the K shell, this binding energy may be considerable. Ultimately, this energy appears as a second electron, since one of the outer-shell electrons will fall into the vacant K orbit and a very soft X-ray may be emitted or a second much slower photo-electron ejected (Auger effect). The second mechanism is Compton scattering, and in this the least-tightly bound electrons are the most likely to be ejected. The energy of the Compton-recoil electron depends on the angle of scatter, but it should be noted that the scattered photon may still have a very high energy and that the chances of absorption of such quanta will not be large in systems of small volume. Not all the energy of the incident quantum is dissipated in the medium. The third mechanism is the creation of positron-electron pairs. This is only possible for photons of energy greater than $2m_0c^2$, where m_0 is the electronic rest mass and c the velocity of light, *i.e.*, ~ 1 Me.v.

⁴⁶ W. H. Bragg, "Studies in Radioactivity," p. 43, London, 1912.

* Coherent scattering and nuclear interaction are here neglected.

The photon is completely converted into an electron and a positron, between which the excess energy of the photon above $2m_0c^2$ is approximately equally divided. The positron is quickly destroyed with another electron giving rise to a γ -ray photon (so-called annihilation radiation) of much lower energy than the original photon, which is therefore absorbed by one of the two other mechanisms.

The existence of these three possible types of γ -ray absorption, each dependent on wave-length in a different way, makes determination of the extinction coefficient for each wave-length very complicated. The Compton scattering coefficients per electron, which are independent of atomic number, can be calculated from the Klein-Nishina formula.⁴⁷ The total absorption coefficient per g. can be measured and hence, if the chemical composition of the material is accurately known, the photoelectric absorption coefficient can be evaluated by difference. The latter coefficients have been related empirically to wave-length and atomic number, and thus the total absorption coefficient for a medium of such a nature that it cannot be measured can be calculated from the sum of the *calculated* Compton coefficient and the *empirical* photo-electric coefficient.⁴⁸

Whatever the magnitude of the γ -ray wave-length, the energy of the photon is converted, if only in part, into a fast electron, which will dissipate this energy along its track by the mechanism already described.

3 (ii). The mean energy to create an ion pair (W). The number of ion pairs formed per unit time in an ionisation chamber can be counted, provided that the system permits the attainment of a saturation current. If the rate of energy absorption is also known, the average amount of energy dissipated in the medium when an ion pair is formed (W) can be readily calculated. Accurate values are known for α -particles in gases of low dielectric constant and vary from 35 ev. in nitrogen to 20.8 ev. in xenon. The values for electrons⁴⁹ are of the same order of magnitude, but increase somewhat as the energy falls below 5 ke.v. The values for X - and γ -rays should be those appropriate to the Compton-recoil electrons, or photo-electrons. These values have been critically discussed by L. H. Gray,³⁶ who selected 32.5 ev. as the appropriate value for air.

The value of W is of great practical and theoretical importance. Its practical significance lies in the fact that many systems, notably liquids, exist for which the rate of energy input can be determined, but in which saturation currents are unattainable. In order to find the rate of ion-pair formation and hence compute the ionic yield, a value of W must be assumed. This is usually taken to be the value for air, appropriate to the radiation employed. In the case of water, for example, the ratio of the volume absorption coefficients of air and water for X -rays can be calculated [see section 3 (i)], and this will also be the ratio of the rates of ion-pair formation in the two media exposed to the same source under identical con-

⁴⁷ O. Klein and Y. Nishina, *Z. Physik*, 1929, **52**, 853.

⁴⁸ See Appendix to ref. 4 for further details.

⁴⁹ W. Gerbes, *Ann. Physik*, 1935, **23**, 648; 1937, **30**, 169.

ditions, *provided that* $W^{\text{XH}_2\text{O}} = W^{\text{Xair}} = 32.5$ ev. On this basis, 1 roentgen of radiation corresponds to the formation of 2.1×10^9 ion pairs c.c.⁻¹ in air and 1.8×10^{12} ion pairs c.c.⁻¹ in water. Unfortunately, the effect of phase change on the value of W can be only conjectured.⁵⁰

Measured values of W for various gases vary only slightly from substance to substance and are always considerably greater than, but apparently not simply related to, the ionisation potential of the substance. The first fact is not well understood. Attempts have been made to calculate values of W for nitrogen and neon,⁵¹ but the results are in poor agreement with experiment. U. Fano⁵² has attributed it to increased outer screening in systems which have high ionisation potentials.

3 (iii). The charged species formed in the primary act. (a) *Distribution.* It has been remarked [section 3 (i)] that, for all types of radiation, ionisation takes place along the track of some charged particle, that the ionisation density is larger the slower the particle and therefore increases along the track, and is larger for heavy particles than for lighter particles of the same energy. The positive ions thus formed lie initially in the wake of the ionising agent. The ejected electrons will be scattered in all directions, and, if there are any molecular species present in the system, which have electron affinity, the scattered electrons will be captured after most of their energy has been dissipated. Such electrons may traverse considerable distances before capture, and hence, very shortly after the ionising agent has passed, its track will consist of a high concentration of positive ions, located in a narrow core, and a lower concentration of negative ions, spread throughout a larger volume. The steep concentration, and electrical potential, gradients thus established will cause a general diffusion radially, and interdiffusion leading to charge neutralisation (*q.v.*). The latter effect results ultimately in the destruction of all the ions, unless the experimental arrangement is such that a clearing field is applied.⁶² The tracks of any fast secondary electrons (δ -rays) will have much the same structure. Before charge neutralisation is complete, a finite interval elapses during which both types of ions may decompose, initiate chemical change, or act as nuclei for clustering of polarisable molecules. The elucidation of the nature of the primary act includes the identification of the ions first formed and their possible fates.

(b) *Identification and stability of positive ions.* Depending on the bonding or antibonding character of the electron removed, ionisation may occur alone or may be accompanied by dissociation. The amount of energy

⁵⁰ Estimates of W for liquid phases have been made. Thus G. W. Hutchinson (*Nature*, 1948, **162**, 610) states that W for Ra-C γ -rays in liquid argon is of the same order as the value for gaseous argon, *i.e.*, 25 ev. N. Davidson and A. E. Larsh (*Physical Review*, 1948, **74**, 220) have observed the ionisation of liquid argon by Po α -rays. F. L. Mohler and L. S. Taylor (*J. Res. Nat. Bur. Stand.*, 1934, **13**, 663) give $W = 24$ ev. for liquid CS₂ using 0.27-A. X-rays. Saturation currents have been measured in hexane and light petroleum by W. Stahel (*Strahlentherapie*, 1929, **31**, 582).

⁵¹ E. Bagge, *Ann. Physik*, 1937, **30**, 72.

⁵² *Physical Review*, 1946, **70**, 44.

⁶² Ref. 7, p. 363.

expended in the various cases will differ, and ionisation potential data are therefore of great value. Since in many cases a considerable proportion of the ions formed are due to impact by electrons of moderate velocities, much information is to be gained from conventional mass-spectroscopical studies of the ions formed by electron impact at various energies and pressures. Glockler and Lind⁵³ have summarised much of the data up to 1938 and F. S. Dainton²⁷ has discussed the special case of water vapour where the most important ions are H_2O^+ , H^+ , and OH^+ . As formed, such ions may be metastable and will therefore decompose very rapidly. For instance, J. A. Hipple, E. U. Condon, and co-workers⁵⁴ have shown that many of the ions of saturated hydrocarbons dissociate unimolecularly with half lives of the order of 10^{-6} sec. into free radicals and carbonium ions or into a paraffin molecule and an olefin ion. Thus, $\text{C}_4\text{H}_{10}^+ \longrightarrow \text{CH}_3 + \text{C}_3\text{H}_7^+$ or $\longrightarrow \text{CH}_4 + \text{C}_3\text{H}_6^+$, and the carbonium ions may spontaneously dehydrogenate, e.g., $\text{C}_3\text{H}_7^+ \longrightarrow \text{C}_3\text{H}_5^+ + \text{H}_2$. Alternatively, the positive ion may react with a neutral molecule, either in an electron-transfer reaction when the ionisation potentials are suitable, e.g., N_2^+ (17 ev.) + NH_3 (11 ev.) $\longrightarrow \text{N}_2 + \text{NH}_3^+$ + 6 ev.,⁵⁵ or in a mass transfer, e.g., $\text{H}_2\text{O}^+ + \text{H}_2\text{O} \longrightarrow \text{H}_3\text{O}^+ + \text{OH}$.⁵⁶

When fast nuclei are employed as the radiation, some of the ionisation is of a primary character [see 3 (i)] and the relevant information in this case will no doubt be forthcoming from mass spectrographs, now being developed, in which the ionisation occurs by impact of fast positive ions such as H^+ , H_2^+ , He^+ .⁵⁷ All mass-spectroscopical data refer to gaseous systems at low pressures. There can be little doubt that, at higher pressures or in condensed systems, aggregation of neutral molecules round ions will occur. In gases, these are known as "clusters"^{6, 7} (see section 5) and should be manifested in unusually small ionic mobilities. Such low mobilities have been observed,⁵⁸ but could equally well be explained by ion-induced dipole forces established between the ion and the polarisable molecules in whose vicinity they move.⁵⁹

(c) *Negative ions*.⁶⁰ Electron capture by neutral atoms and molecules only occurs with slow electrons and when the neutral entities have appreciable electron affinity. Unfortunately, there are few mass-spectroscopical data on negative ions, and most of the information is obtained from electron "swarm" experiments,⁶¹ from which it appears that 1Σ diatomic molecules

⁵⁴ J. A. Hipple, R. E. Fox, and E. U. Condon, *Physical Review*, 1947, **69**, 257, and earlier papers referred to therein. Also ref. 12, p. 456.

⁵⁵ S. C. Lind, *J. Amer. Chem. Soc.*, 1931, **53**, 2423.

⁵⁶ H. D. Smyth and D. W. Mueller, *Physical Review*, 1933, **43**, 116.

⁵⁷ J. R. Keene, private communication.

⁵⁸ A. M. Tyndall, "The Mobility of Positive Ions in Gases," Cambridge, 1938.

⁵⁹ L. B. Loeb, "Fundamental Processes of Electrical Discharge in Gases," New York, 1939.

⁶⁰ H. S. W. Massey, "Negative Ions," London, 1938.

⁶¹ A. M. Crovath, *Physical Review*, 1929, **33**, 605; N. E. Bradbury, *ibid.*, 1933, **44**, 883; F. Bloch and N. E. Bradbury, *ibid.*, 1935, **48**, 689.

do not form negative ions. Even a $^1\Sigma$ molecule may capture an electron, provided that the electron has sufficient energy to dissociate the molecule into fragments, one of which is not in a $^1\Sigma$ state, and therefore becomes the negative ion, *e.g.*, $\text{Cl}_2 + e \longrightarrow \text{Cl} + \text{Cl}^-$.

A further possibility, which does not appear to have been investigated experimentally, is simultaneous formation of positive and negative ions. Such heterolysis would probably require more energy than homolytic fission of the same bond.

In general, less is known about negative ions and their formation, but there is no reason why they should not undergo the same types of reaction as positive ions, namely, breakdown, ion-neutral molecule reaction, clustering, and ultimately, charge neutralisation.

3 (iv). The uncharged species formed in the primary act. (a) *From the ions.* Uncharged entities differing from the molecules of the absorbing medium may be formed by breakdown or reaction of the ions in processes which have been discussed in 3 (ii).

Charge-neutralisation processes are not well understood, but it is conceivable that these also may cause formation of atoms and radicals. The negative charge is unlikely to be a free electron, and we therefore restrict our discussion to ion-ion reactions. If the ions concerned are radical or atomic ions, their union could give a finished molecule, *e.g.*, $\text{H}^\cdot + \text{OH}^\cdot \longrightarrow \text{H}_2\text{O}$, provided a third body is present. The energy released might be degraded to heat energy or used to dissociate the third body. Alternatively, charge neutralisation may be achieved by ionic dismutation, *e.g.*, $\text{C}_2\text{H}_5^- + \text{H}^+ \longrightarrow \text{C}_2\text{H}_4 + \text{H}_2$. Even in such cases there might be considerable energy release. The net effect of any charge-neutralisation process will be to release, in a restricted locality, energy approximately equal to that put in when creating the ion pair. J. O. Hirschfelder⁴¹ has pointed out that this energy is likely to be completely used in immediate dissociation of the molecule on which the energy is located, but, if the molecule has a large number of internal degrees of freedom, this energy may be slowly degraded to heat.⁷²

(b) *Directly.* There are two powerful arguments for the view that some of the reaction is effected through uncharged intermediates. The first is that W is always larger than the ionisation potential. The excess energy, of the order 15 ev., must be dissipated in processes not leading to ionisation. Such processes are likely to be electronic excitation of the molecules, and, in view of the magnitude of the energy involved, it is possible that some of the energy is used to excite the molecule to non-ionic repulsive levels. Estimates of the effectiveness of this process are conjectural.²⁷ The second line of evidence is that H. Essex and co-workers⁶² have shown that the rates of decomposition of nitrous oxide and ammonia induced by α -rays are only slightly reduced when electrical fields are applied which materially reduce the number of ions undergoing charge neutralisation.

⁶² C. Smith and H. Essex, *J. Chem. Physics*, 1938, **6**, 188; A. D. Kolumban and H. Essex, *ibid.*, 1940, **8**, 450; N. T. Williams and H. Essex, *ibid.*, 1948, **16**, 1153.

(c) *Identification of radicals and atoms.* Mass-spectroscopic measurements are not of great value in identifying atoms and radicals formed in the primary act, unless the appearance potentials can be accurately measured and used to discriminate between radical ions formed directly and those formed by ionisation of radicals in the spectrometer. On the other hand, ultra-violet absorption and emission spectra should afford a valuable means of identification, not only of atoms and radicals, but also of molecules and ions. It has already been used to identify hydrogen atoms, and hydroxyl radicals in discharges through water vapour.⁶³ The study of light emission from beams of high specific ionisation would be particularly fruitful in that it would serve to identify any electronically excited species. Surprisingly few spectroscopic observations have been made on ionising radiations, although the luminosity of such beams in air is well known. H. Greinacher⁶⁴ has reviewed previous work and has shown that the intensity of radiation from polonium α -rays in air, carbon dioxide, hydrogen, or oxygen is unaffected by complete discharge of the ions, and increases with pressure, and that, with hydrogen, much of the light emitted is in the ultra-violet region. E. Kara-Michaelova⁶⁵ has established that total light emission of wave-lengths >2000 Å. per element of length of the track of Po α -particles in air, varies with the distance from the end of the range as does the variation of specific ionisation.

W. E. Burcham and F. S. Dainton⁶⁶ have photographed the spectra of the light emitted from an ~ 600 -kv. proton beam. Preliminary results indicate that excited nitrogen molecules are formed in air, but no results have been obtained as yet with water vapour or other gases. Work has also been reported on the light emission of pencils of α -rays passing through mercury or sodium vapour in an excess of nitrogen or helium.⁶⁷ No luminescence associated with excited species has been observed in liquids, although the Čerenkov continuum, which is produced when electrons traverse a medium with a velocity exceeding that of light in the medium, has been investigated in detail.⁶⁸ Chemical tests for atoms and radicals can also be applied. Usually the existence of such reactive intermediates is suggested by features of the kinetics of the reaction, *e.g.*, very large ionic yields, or polymerisation.

(d) *Distribution.* Atoms and radicals formed by rapid decomposition of metastable ions or by efficient reaction with neutral molecules will have an initial distribution very similar to that of the parent ions [section 3 (iii) (a)].

⁶³ K. Bonhoeffer and T. G. Pearson, *Z. physikal. Chem.*, 1931, **B**, **14**, 1; G. I. Lavin and F. B. Stewart, *Nature*, 1929, **123**, 607; O. Oldenburg *et al.*, *J. Chem. Physics*, 1939, **7**, 485, and earlier papers.

⁶⁴ *Z. Physik*, 1928, **47**, 344.

⁶⁵ *Sitzungsber. Akad. Wiss. Wien, Klasse 2A*, 1934, **143**, 15.

⁶⁶ Unpublished.

⁶⁷ A. Luyckx and J. Bodart, *Physica*, 1943, **10**, 79.

⁶⁸ L. Mallet, *Compt. rend.*, 1926, **183**, 274; 1929, **188**, 445; P. A. Čerenkov, *Physical Review*, 1937, **52**, 378; G. B. Collins and V. E. Reiling, *ibid.*, 1938, **54**, 499; H. O. Wyckoff and J. E. Henderson, *ibid.*, 1943, **64**, 1; P. B. Weisz and B. L. Anderson, *ibid.*, 1947, **72**, 431.

Thus, all the radicals derived from positive ions will be situated along the axis of the track, whereas those derived from the negative ions will be more widely distributed. Uncharged species which are formed by direct excitation [section 3 (iv) (b)] may be widely spread or confined to the centre of the track, depending on whether the lifetime of the excited levels of the parent molecule is long or short. Radicals which have their origin in charge neutralisation reactions will almost certainly be widely spread. It is important to remember that those formed from metastable ions will be commonly of the same chemical nature when derived from ions of the same charge, whereas direct excitation and charge neutralisation produce several radicals, not necessarily identical, which could, under suitable conditions, recombine to form the original molecule.

(e) *Number.* The total number of uncharged species formed when a certain amount of energy is absorbed is of great importance. It is also a very elusive quantity and, like the quantum yield of the primary photochemical act, has an upper limit. For example, if H and OH are the only products of the primary act in water vapour, it is certain that not more than six of each of these radicals can be formed per 32.5 ev. of energy absorbed. The fraction of these which ultimately cause the observed reaction is probably less, and will depend on the nature of the reaction. Once the identities of the products of the primary act have been revealed, it should be possible to estimate their number from the magnitude of the reaction which they cause with a reagent of known reactivity.²⁷

3 (v). The effect of the state of aggregation on the primary act.⁶⁹ The great increase in density associated with liquefaction will have several important consequences. First, the methods available to identify the intermediates are almost exclusively chemical tests. Secondly, the primary act may be profoundly affected.²⁷ The specific ionisation will be much higher, and the mean energy, W , and ionisation potentials may be altered, although there is no direct evidence on the latter point.⁵⁰ Deactivational possibilities will be enhanced and the persistence of excited species will therefore be less. If the liquid is polar, the effects of solvation will modify the stability of any ions formed and their probability of being transformed into radicals. Exothermic recombination processes, of ions and radicals alike, will be facilitated by the nearness of third bodies. Immediate recombination by the Franck-Rabinowitch mechanism,⁷⁰ of fragments formed from the same molecule by direct dissociation [3 (iv) (b)] will also play a part. The overall effect may be that the number of species capable of effecting decomposition of a pure liquid or reacting with a solute is much reduced and that the products of decomposition of a pure liquid arise principally from the radicals formed from the ions [3 (iv) (a)]. The latter distinction has been drawn in a somewhat different form and emphasis by A. O. Allen in the case of liquid water.⁷¹

⁶⁹ See also M. Burton, ref. 12, p. 575.

⁷⁰ J. Franck and E. Rabinowitch, *Trans. Faraday Soc.*, 1934, **70**, 120.

⁷¹ Ref. 12, p. 479.

Any energy which is not used in chemical change or light production will appear as heat which will be manifested as a temperature rise. F. H. Krenz⁷² has detected this dilatometrically in the case of liquid water irradiated with γ -rays. A feature of this effect is its persistence for about a minute after the irradiation is stopped. This after-effect is attributed by the author to the slowness of the degradation of the internal energy into heat, which would be expected if the internal energy was originally excitational energy of complex units. Krenz identifies these units with water polymers. The same lag would be expected in all associated liquids, not only as an after-effect, but also as an induction period to the expansion. Moreover, as the author points out, such lags should not be observed in relatively unassociated liquids, but might occur when polymeric compounds are dissolved in them. This behaviour is exemplified by benzene, which alone shows no lag, whereas 1% solutions of polystyrene in benzene show a short lag. These observations are of great interest and, if extended, might yield interesting information concerning the structure of liquids. It is to be hoped that the influence of temperature will be investigated, since this should reduce the number and complexity of the water polymers, but not affect the polystyrene solute molecules, and would thus discriminate between the two systems.

3 (vi). A similar division into primary and secondary processes is made in photochemistry. The two subjects are similar only in respect of secondary processes. In all other respects they differ very widely.⁷³

4. Secondary Processes, Ionic Yield, and the "Cluster" Theory.—In the preceding section, emphasis was laid on the view that, chemically, the most important products of the primary act are the uncharged atoms and radicals. An alternative hypothesis, formerly widely held, is the "cluster theory" in which uncharged species are disregarded and the ions regarded as the more important. The essence of the cluster theory, as proposed by S. C. Lind,^{6, 7} is that one or both members of an ion pair act as nuclei, to which neutral molecules are drawn and held as clusters by polarisation forces. Reaction was conceived as occurring on charge neutralisation, *all* the molecules of the complex undergoing chemical change and the requisite energy of activation being provided by the heat of neutralisation. For example, the oxidation of methane was written as $(\text{O}_2\text{CH}_4\text{O}_2)^+ + (\text{O}_2^-\text{CH}_4\text{O}_2) \longrightarrow 2\text{CO}_2 + 4\text{H}_2\text{O}$. Such a theory is clearly capable of accounting for ionic yields slightly in excess of unity, and for the usual kinds of variation of M/N with pressure, since the size of the cluster will be related to the initial pressure. In its simple form, specific ion clusters were assumed and designated,⁷⁴ but later work by W. Mund,⁷⁵ E. K. Rideal,⁷⁶ and R. S. Livingston⁷⁷ has been concerned with the nature of the inter-

⁷² F. H. Krenz, *Canadian J. Res.*, 1948, **26**, 647.

⁷³ F. S. Dainton, *Research*, 1948, **1**, 488.

⁷⁴ See, e.g., ref. 6, table VIII, p. 100. ⁷⁵ *Bull. Soc. chim. Belg.*, 1934, **43**, 100.

⁷⁶ *Troisième Conseil chim. Solway*, 1928, **1**.

⁷⁷ *Bull. Soc. chim. Belg.*, 1936, **45**, 334.

action of the central ion with its surrounding molecules. The main evidence for clusters has been recently reviewed.⁷⁸

Whilst values of ionic yields calculated on the cluster theory are claimed to be in quantitative agreement with experiment,⁷⁹ and whilst the average distribution in the system will include some aggregation of molecules around charges, there are several major objections to adopting the cluster theory as a general mechanism for radiochemical reactions. Thus, (a) Essex and co-workers⁶² have shown that, under conditions where ion neutralisation is eliminated or considerably reduced, the ionic yield is only slightly affected, and (b) excitational processes leading to, and experimental evidence for, uncharged atoms and radicals known to induce the chemical change observed have no place in the theory.

In the ensuing pages the "atom-radical" theory of the primary act will be most frequently employed and it will be assumed that the secondary processes are merely those reactions into which the uncharged products of the primary act would enter whatever their mode of formation—thermal, photochemical, or radiochemical. This "carry over" of information from one investigation to the interpretation of another has been discussed by E. W. R. Steacie.⁷⁹

The number of reactions which have been stimulated by radiation is very large and the reactions mentioned in this Report have been chosen either because the primary act is well understood and exemplifies principles already mentioned, or because the observed kinetics have no parallel with other modes of initiation, or because the reaction is intrinsically important and recent work has clarified a previously obscure mechanism.

5. Single Inorganic Substances (excluding Water).—The decomposition of solid and gaseous inorganic substances has been extensively investigated.^{6, 7, 9} No coherent theory exists for the former, except where the solids can be detonated by impact, *e.g.*, nitrogen tri-iodide⁸⁰ and barium azide.⁸¹ Hydrogen iodide has been studied in all three phases.⁸² In the gaseous phase the oxygen-ozone system,⁸³ the oxides of nitrogen,⁸⁴ and various hydrides, *e.g.*, NH_3 ,⁶² ND_3 ,⁸⁵ HI ⁸² and H_2S ⁸⁶ have been much studied. A feature of many of these reactions is that the ionic yield exceeds

⁷⁸ R. S. Livingston and S. C. Lind, *J. Amer. Chem. Soc.*, 1936, **58**, 612; S. C. Lind, ref. 12, p. 437, and *J. Chem. Physics*, 1939, **7**, 790.

⁷⁹ Ref. 12, p. 441.

⁸⁰ M. Haissinsky and R. J. Walen, *Compt. rend.*, 1939, **208**, 2067; E. Feenberg, *Physical Review*, 1939, **55**, 980.

⁸¹ W. E. Garner and C. H. Moon, *J.*, 1933, 1398.

⁸² P. Günther *et al.*, *Ber.*, 1943, **75**, B, 2064; Günther and Leichter, *Z. physikal. Chem.*, 1936, B, **34**, 443; K. G. Brattain, *J. Physical Chem.*, 1938, **42**, 617.

⁸³ S. C. Lind, *Monatsh.*, 1912, **32**, 295; P. C. Capron and R. Cloetens, *Bull. Soc. chim. Belg.*, 1935, **44**, 441; B. Lewis, *J. Physical Chem.*, 1933, **37**, 533.

⁸⁴ G. R. Gedye, *J.*, 1931, 3016; W. Mund and R. Gillerot, *Bull. Soc. chim. Belg.*, 1929, **38**, 349.

⁸⁵ J. C. Jungers, *J. Physical Chem.*, 1936, **40**, 155.

⁸⁶ W. Mund *et al.*, *Bull. Soc. chim. Belg.*, 1934, **43**, 49, 100; 1937, **46**, 129; P. Calmont, *ibid.*, 1932, **41**, 431.

unity and is several times larger than the quantum yield of the corresponding photochemical reaction, which is strongly suggestive of more than one radical being formed per ion-pair.⁸⁷

The spin isomerisation of hydrogen under the influence of α -rays has a very large ionic yield, 800—1000, too great to be accounted for by clustering and strongly suggestive of a chain mechanism. P. C. Capron¹⁷ found the rate of destruction of para-hydrogen by α -particles from radon in a spherical vessel to be given by

$$-d[pH_2]/dt = -ke^{-\lambda t} \cdot [pH_2] \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where λ is the decay constant of radon. The ionic yield is therefore independent * of the dose rate and any reaction chain cannot undergo mutual termination, a result which is somewhat surprising since in the high-temperature thermal conversion it is certain that the chains are stopped in pairs by recombination of hydrogen atoms.⁸⁸ Capron therefore considered the possibility of the chain carrier being a proton, but, since no reactions occurred at -187° , he suggested that a hydrogen *atom* is the effective agent. Reproducible results were obtained in the presence of mercury vapour which Capron found to be a retarding agent. These kinetic results could be explained by assuming the reaction sequence, (i) $H_2 \xrightarrow{\alpha} 2H$, (ii) $H + pH_2 \rightleftharpoons oH_2 + H$, (iii) $H + Hg \longrightarrow HgH$, but H. Eyring, J. O. Hirschfelder, and H. S. Taylor⁸⁹ have calculated the equilibrium constant of reaction (iii) and find that, at the partial pressures of mercury concerned, this reaction cannot be regarded as an efficient process for removal of atomic hydrogen. They therefore conclude that the major termination reaction is removal of atomic hydrogen at the vessel walls. If a perfectly efficient wall removal was assumed and since the dimensions of the reaction vessel and source, the velocity constant of the propagation reaction (ii),⁸⁸ and the diffusion constant of atomic hydrogen through molecular hydrogen were known, a rate of formation of hydrogen atoms could be calculated which accounted for the observed reaction rates, *provided* that six hydrogen atoms were formed per 33 ev. of α -ray energy absorbed.

The most important feature of these authors' work is that it contains the first close theoretical analysis of a primary act. Equilibrium distribution of doublet ($H_2 H_2^+$) and triplet ($H_2 H_2^+ H_2$) clusters are calculated on reasonable assumptions, and the values indicate that larger clusters are improbable. The ion H_2^+ is regarded as constituting upwards of 90% of the primary ionisation. The velocity constant of the reaction (iv), $H_2^+ + H_2 \longrightarrow H_3^+ + H$, is calculated to be 1.25×10^{15} c.c. mole⁻¹ sec.⁻¹, and this reaction therefore predominates at reasonable pressures. The neutral-

⁸⁷ Ref. 4, table XX; ref. 27, table I.

⁸⁸ A. Farkas, *Z. physikal. Chem.*, 1930, 10, B, 419.

⁸⁹ *J. Chem. Physics*, 1936, 4, 479.

* Note that Eyring *et al.* (ref. 4, p. 491) mistakenly remark that "the M/N yield was dependent on the radon intensity, etc."

isation reaction of H_3^+ with an electron is considered to yield between 2 and 3 hydrogen atoms. Hence the total net yield of hydrogen atoms from the ion pair $H_2^+ + \text{electron}$ is between 3 and 4 [cf. section 3 (iv) (a)]. The part of W ($= 33$ ev.) not used in ionisation is regarded as causing excitation of hydrogen molecules ($^1\Sigma \longrightarrow ^3\Sigma$), a process which requires 12 ev., and results in dissociation of the hydrogen into two hydrogen atoms.

6. Binary Inorganic Mixtures.—When one component, the solvent, is in great excess, the products of the primary act will be derived largely from that component. When the chemical change observed is due solely to reaction of these products with the solute, it is referred to as "indirect action" of the radiation [cf. section 3 (v)]. Few examples are known of indirect action on systems in which both components are inorganic.⁹⁰ Hydrazine, at concentrations of 0.05 to 0.1% in hydrogen, is reduced to ammonia by the action of α -rays from radon, with an ionic yield of 3.⁹¹ The mechanism suggested includes: $H_2 \xrightarrow{\text{radiation}} 2H$; $N_2H_4 + H \longrightarrow NH_2 + NH_3$; $2NH_2 + M \longrightarrow N_2H_4 + M$. Decomposition of hydrazine and hydrogen sulphide by indirect action is also possible in excess of nitrogen, but in this case the mechanism is less well understood. P. Gunther and L. Holzapfel⁹² have studied the decomposition of ammonia, and the synthesis of water, by indirect action of X-rays in an excess of xenon. A radical mechanism is here difficult to formulate. Some of the reaction is doubtless due to collisions of excited xenon atoms with the reactants and may result in the dissociation of the latter. The point has also been made by H. Eyring⁹³ that the xenon ion is electronically merely a very reactive form of an iodine atom. Part of the reaction in this case might therefore be represented as $Xe^+ + NH_3 \longrightarrow (XeH)^+ + NH_2$.

Most radiochemical reactions in inorganic mixtures are systems in which both reactants make their contributions to the primary act, which is therefore rather complex. The reactions investigated include *addition* reactions, $H_2 + Cl_2 \rightleftharpoons 2HCl$,⁹⁴ $H_2 + Br_2 \rightleftharpoons 2HBr$,^{79, 95} $H_2 + I_2 \rightleftharpoons 2HI$,⁸² $CO + Cl_2 \rightleftharpoons COCl_2$,⁹⁶ $CO + 0.5O_2 \rightleftharpoons CO_2$;⁹⁷ isotopic exchange reactions, *e.g.*, $H_2 + D_2 \rightleftharpoons 2HD$;⁹⁸ and many oxidations, *e.g.*, $C_nH_{2n+2} + O_2$,⁹⁹ $N_2 + O_2$.¹⁰⁰ Many of these, particularly those involving halogens, have

⁹⁰ The first investigators to achieve indirect action through hydrogen were W. Duane and G. L. Wendt (*Physical Review*, 1917, **10**, 116).

⁹¹ A. van Tiggelen, *Bull. Soc. chim. Belg.*, 1938, **47**, 577.

⁹² *Z. physikal. Chem.*, 1937, **38**, B, 211.

⁹³ *J. Chem. Physics*, 1939, **7**, 792.

⁹⁴ F. Porter, D. C. Bardwell, and S. C. Lind, *J. Amer. Chem. Soc.*, 1926, **48**, 2603; S. C. Lind and R. S. Livingston, *ibid.*, 1930, **52**, 593; S. Götzky and P. Günther, *Z. physikal. Chem.*, 1934, **26**, B, 373.

⁹⁵ E. F. Ogg, *J. Physical Chem.*, 1939, **43**, 399.

⁹⁶ H. N. Alyea and S. C. Lind, *J. Amer. Chem. Soc.*, 1930, **52**, 1853.

⁹⁷ S. C. Lind and C. Rosenblum, *Proc. Nat. Acad. Sci.*, 1932, **18**, 374.

⁹⁸ W. Mund, L. Kaertkemeyer, M. Vanpee, and A. van Tiggelen, *Bull. Soc. chim. Belg.*, 1940, **49**, 187.

⁹⁹ Lind and Bardwell, *J. Amer. Chem. Soc.*, 1926, **48**, 2335.

¹⁰⁰ R. Cloetens, *Bull. Soc. chim. Belg.*, 1936, **45**, 97.

photochemical counterparts which are chain reactions, and the similarity of kinetics suggests the participation of halogen atoms as chain centres. In several cases, detailed analysis of the primary act has shown that the atoms are formed at this stage, of a kind and number to enable quantitative interpretation of the experimental results.¹⁰¹

7. Single Organic Substances.—Much qualitative work on the stability of organic compounds to rays from radium was carried out by A. Kailan.¹⁰ Many of his experiments were conducted with access to air and with wet materials. Nevertheless, the essential features of the radiolysis were detected and have been confirmed by later work. Saturated compounds tend to break at a weak bond and to lose some easily eliminated group. If the remaining fragment is a radical, it may dimerise, and, if it is an unsaturated molecule, it will be polymerised. Thus the paraffins are dehydrogenated and the residue consists of liquid hydrocarbons, whether α -particles⁹⁹ or high-speed electrons¹⁰² are used. Similarly, alcohols yield hydrogen and polymerised aldehydes¹⁰³ amongst the products. Irradiation of chloroform by γ - or X-rays causes evolution of chlorine in the initial stages of reaction.¹⁰⁴ Reabsorption of some of the chloride with formation of hydrochloric acid and hexachloroethane may occur subsequently.

Unsaturated compounds, *e.g.*, olefins,¹⁰⁵ cyanogen,¹⁰⁶ carbonyl¹⁰³ and vinyl compounds²⁹ polymerise as freely under irradiation as by any other initiating action. The polymerisation of acetylene has been very closely studied because it appeared to be a clear example of a reaction proceeding by the ion-cluster mechanism.¹⁰⁷ The evidence for this view as against the normal radical-type chain polymerisation was principally the apparent constancy of the ionic yield = 20 over a wide variety of conditions, including the presence of non-reactive diluents such as the inert gases or nitrogen. The mechanism, suggested by Lind, was that 19–20 acetylene molecules clustered about either a $C_2H_2^+$ ion or an inert-gas ion. On neutralisation the whole complex was supposed to liberate, as the only product, a solid yellow polymer of formula $(C_2H_2)_{20}$. Substantially the same results were obtained and the same mechanism proposed for dideuteroacetylene, C_2D_2 .¹⁰⁸ The insolubility of the product prevented determination of its molecular

¹⁰¹ H. Eyring, J. O. Hirschfelder, and H. S. Taylor, *J. Chem. Physics*, 1936, **4**, 590; 1938, **6**, 783.

¹⁰² C. S. Schoepfle and C. H. Fellows, *Ind. Eng. Chem.*, 1931, **23**, 1398.

¹⁰³ J. C. McLennan and W. L. Patrick, *Canadian J. Res.*, 1931, **5**, 470.

¹⁰⁴ W. B. S. Bishop, *J. Proc. Sydney Tech. Coll. Chem. Soc.*, 1933, **5**, 66, quoted in *Chem. Abs.*, 1934, **28**, 2272; G. Harker, *Nature*, 1934, **133**, 378.

¹⁰⁵ G. B. Heisig, *J. Amer. Chem. Soc.*, 1931, **53**, 3245; *J. Physical Chem.*, 1935, **39**, 1067; 1939, **43**, 1207.

¹⁰⁶ D. C. Bardwell, J. M. Perry, and S. C. Lind, *J. Amer. Chem. Soc.*, 1926, **48**, 1556.

¹⁰⁷ Ref. 6, G. Glockler and F. W. Martin, *Trans. Electrochem. Soc.*, 1938, **74**, 67; J. C. McLennan, M. W. Perrin, and H. J. C. Ireton, *Proc. Roy. Soc., A*, 1929, **125**, 246; W. Mund, C. Velghe, C. Devos, and M. Vanpee, *Bull. Soc. chim. Belg.*, 1939, **48**, 269.

¹⁰⁸ S. C. Lind, J. C. Jungers, and C. H. Schiflett, *J. Amer. Chem. Soc.*, 1935, **57**, 1032.

weight. Recently, it has been shown that the electron micro-photographs of this material are not those expected of a substance $C_{40}H_{40}$.¹⁰⁹ Moreover, this is not the only product of reaction. Benzene is also formed, and under suitable conditions it may represent as much as 20% of the product.¹¹⁰ Although these facts render the original cluster hypothesis for this reaction untenable, they do not necessarily exclude an ionic mechanism,¹¹¹ which appears to be the preferred method when unsaturated hydrocarbons are polymerised.¹¹²

8. Binary Organic Mixtures.—Very little systematic work has been published in this field. Direct action has been observed,¹¹³ and indirect action with an organic compound as solute¹¹⁴ or solvent.¹¹⁵

9. Water and Dilute Aqueous Solutions.—The action of radiations on water is of great importance, for both its intrinsic interest and its relevance to the study of the biological action of radiations.⁴ All the peculiar features of radiochemical reactions, *e.g.*, radiochemical equilibrium, indirect action, influence of track density, etc., are here displayed. Several reviews are available.¹¹⁶

(i) **Experimental results.** (a) *Ice, Water, and Steam.* X-Rays have no action on ice, unless it contains oxygen, when hydrogen peroxide is formed. The yield decreases with temperature, becoming zero at -116° .¹¹⁷ On the other hand, α -rays decompose ice even in the absence of oxygen, with an ionic yield of about 0.05 to 0.1 molecule of water destroyed per 35 ev. absorbed. This reaction does not appear to be temperature dependent, but, whereas P. Bonet-Maury¹¹⁷ claims that the product is H_2O_2 , W. Duane and O. Scheuer¹¹⁸ stated that this is exclusively hydrogen and oxygen. Water vapour appears to be even less affected by α -rays, Duane and Scheuer finding an ionic yield of about 0.01. However, electrons appear to bring about speedy decomposition. Thus the xenon-sensitised X-radiolysis¹¹⁹ results in formation of much hydrogen in unit yield in amounts strictly proportional to the dose. Likewise, cathode rays rapidly set up the equilibrium, $2H_2O \rightleftharpoons H_2O_2 + H_2$.¹²⁰ In addition, there is much spectro-

¹⁰⁹ J. H. L. Watson, *ref. 12*, p. 470.

¹¹⁰ C. Rosenblum, *ref. 12*, p. 474.

¹¹¹ W. M. Garrison, *J. Chem. Physics*, 1947, **15**, 78.

¹¹² See, *e.g.*, C. E. H. Bawn, "The Chemistry of High Polymers," London, 1948.

¹¹³ *E.g.*, Halogenation of $CO\cdot$ and C_6H_6 ; *ref. 6* and H. N. Alyea, *J. Amer. Chem. Soc.*, 1930, **52**, 2743.

¹¹⁴ P. Günther and H. Theobald, *Z. physikal. Chem.*, 1938, **40**, B, 1.

¹¹⁵ L. Baumeister and R. Glocker, *ibid.*, 1921, **97**, 368; E. Broda, *Nature*, 1943, **151**, 448.

¹¹⁶ C. B. Allsopp, *Trans. Faraday Soc.*, 1944, **40**, 79; O. Risse, *Ergebn. Physiol.*, 1930, **30**, 242; H. Fricke, *Cold Spring Harbor Symp.*, 1935, **3**, 55.

¹¹⁷ P. Günther and L. Holzapfel, *Z. physikal. Chem.*, 1939, **44**, B, 374; P. Bonet-Maury and M. Lefort, *Nature*, 1948, **162**, 381.

¹¹⁸ *Radium*, 1913, **10**, 33; *Compt. rend.*, 1913, **156**, 466.

¹¹⁹ P. Günther and L. Holzapfel, *Z. physikal. Chem.*, 1939, **42**, B, 346.

¹²⁰ M. Kernbaum, *Radium*, 1910, **7**, 242.

scopical and mass-spectroscopical data on the break up of water by slow-electron bombardment and in discharges.¹²¹

Many of the thirty-five or so papers which have been published on *water* appear to contain contradictory results. The reasons for this are the profound effect exerted by dissolved air, the existence of a radiation-sensitised back reaction, and the inherent instability of one of the reaction products. Despite such difficulties the following facts have been established. (a) Water containing dissolved oxygen is converted into hydrogen peroxide, whatever type of radiation is used,¹²² and there is evidence that the amount of H_2O_2 so formed is proportional to the dose and increases with the concentration of oxygen present initially and with temperature. (b) The extent of reaction is less in ice than in water, and there is thus a discontinuity in the yield at 0° .^{117, 118} (c) By use of carefully de-aërated water and massive radiation, *i.e.*, α -rays, the products of reaction are hydrogen peroxide and sometimes oxygen, in amounts which together are equivalent to the hydrogen evolved.^{71, 123} The yield does not appear to depend on temperature but decreases abruptly on freezing.¹¹⁷ (d) When X - or γ -rays or fast electrons are the radiation employed, the hydrogen peroxide concentration formed is very low, and in some cases undetectably small.¹²⁴ (e) Certain compounds within a very wide range of chemical substances, when added to water, raise the H_2O_2 concentration enormously, without necessarily being affected themselves.^{89, 125} (f) Hydrogen and hydrogen peroxide are the primary products, and oxygen is formed, not initially, but as the result of some secondary processes.⁷¹

(b) *Dilute Aqueous Solutions.* Irradiation of solutions containing reducing agents leads to liberation of hydrogen and oxidation of the solute, *e.g.*, Fe^{++} salts \longrightarrow Fe^{+++} salts;¹²⁶ nitrites \longrightarrow nitrates.¹²⁷ The presence of dissolved oxygen increases the rate of oxidation and prevents evolution of hydrogen; but, as soon as the oxygen is exhausted, the rate falls to the value appropriate to de-aërated water and the evolution of hydrogen commences.^{37, 128} If the solute is an oxidising agent, *e.g.*, ceric sulphate, potassium dichromate, it is reduced and oxygen is evolved; or, if the solute is organic, *e.g.*, formic acid, carbon dioxide may be produced. When neither oxygen nor hydrogen are detected, it is usually because the solute

¹²¹ For references see Dainton, *ref. 12*, p. 517.

¹²² F. L. Usher, *Jahrb. Rad. Elekt.*, 1911, **8**, 323; O. Risse, *Z. physikal. Chem.*, 1929, **140**, 133; H. Fricke, *J. Chem. Physics*, 1934, **2**, 556; J. Loiseleur, R. Latarjet, and T. Caillot, *Compt. rend.*, 1941, **213**, 730; Bonet-Maury and Lefort, *ref. 117*.

¹²³ C. E. Nurnberger, *J. Physical Chem.*, 1937, **41**, 431.

¹²⁴ O. Risse; ¹²² H. Fricke and F. R. Brownscombe, *Physical Review*, 1933, **44**, 240; H. Fricke; ¹²² Piffault, *Compt. rend. Soc. Biol.*, 1939, **130**, 43; Günther and Holzapfel; ¹¹⁹ Loiseleur *et al.*; ¹²² Bonet-Maury; ¹¹⁷ A. O. Allen.⁷¹

¹²⁵ H. Fricke and E. J. Hart, *J. Chem. Physics*, 1935, **3**, 596.

¹²⁶ H. Fricke and S. Morse, *Phil. Mag.*, 1929, **7**, 129; H. Fricke and E. J. Hart, *J. Chem. Physics*, 1935, **3**, 60.

¹²⁷ H. Fricke and E. J. Hart, *ibid.*, 1935, **3**, 365.

¹²⁸ N. A. Shishakov, *Phil. Mag.*, 1932, **14**, 198.

undergoes neither reduction nor oxidation, *e.g.*, it may be polymerised or hydrolysed. The magnitude of the chemical change is often proportional to the dose and independent of solute concentration over wide ranges.^{125, 127} For example, this is true of the enzyme carboxy-peptidase, even when it is present to the extent of 14% by weight. This constancy of ionic yield is proof that under these conditions the change in the solute is due to the rate of energy absorption in the solvent, *i.e.*, that the action is *indirect* (cf. section 6). However, there is also evidence that a critical concentration exists, below which the ionic yield decreases with falling solute concentration.^{129, 130} It also seems likely that (a) in the concentration range where M/N is constant, different types of radiation may be associated with different ionic yields,¹³¹ and (b) the value of the critical concentration is determined partly by the nature of the solute and partly by the nature of the radiation. Certain solutes, notably large organic molecules of biological importance, subject to indirect action at concentrations above any real or hypothetical critical value decay exponentially (*i.e.*, according to a first-order law) throughout a run.¹³² This suggests the interpretation, now accepted, that only that part of the effect of the radiation on the water which is proportional to the percentage of solute remaining is transmitted to the solute. The remainder of the energy is therefore assumed to be transmitted to the soluble product into which the reactant is converted.¹³³ When two or more solutes of comparable concentration and reactivity are present, there is competition between them; when they are of different reactivity, the more reactive is transformed preferentially, thereby protecting the less reactive.¹³⁴ Few data are available concerning the effect of temperature¹³⁵ and dose rate.³⁷

(ii) **Interpretation.** Most of the data summarised above can be interpreted on a non-cluster mechanism.

(a) *The Primary Act.* It was first suggested by O. Risse in 1929¹³⁶ that the assumption that X-rays dissociate water into hydrogen atoms and hydroxyl radicals and that these species then dimerise, would account for the formation of hydrogen peroxide and hydrogen and for the doubling of the ionic yield in the X-ray oxidation of ferrous sulphate solution by dissolved oxygen. In the same year the capacity of water vapour containing hydrogen atoms and hydroxyl radicals to behave in the dual role of both an oxidising and a reducing agent was recognised by G. I. Lavin and F. B. Stewart.⁶³ During the following decade the investigations of J. Weiss

¹²⁹ H. Fricke, E. J. Hart, and H. P. Smith, *J. Chem. Physics*, 1938, **6**, 229.

¹³⁰ W. Stenström and A. Lohmann, *J. Biol. Chem.*, 1928, **79**, 673.

¹³¹ L. H. Gray, W. M. Dale, and W. J. Meredith, private communication.

¹³² H. Fricke and B. W. Peterson, *Amer. J. Roentgenol.*, 1927, **17**, 611.

¹³³ W. M. Dale, W. J. Meredith, and M. C. K. Tweedie, *Nature*, 1943, **151**, 281.

¹³⁴ W. M. Dale, *Biochem. J.*, 1942, **36**, 80.

¹³⁵ T. Alper, *Nature*, 1948, **162**, 615; W. Minder and A. Liechti, *Experientia*, 1946, **2**, 410.

¹³⁶ *Strahlentherapie*, 1929, **34**, 581.

and others¹³⁷ demonstrated the existence of ready electron-transfer processes involving hydrogen atoms or hydroxyl radicals in aqueous media, and in 1944 Weiss¹³⁸ proposed that the hydrogen atoms and hydroxyl radicals present in water subjected to irradiation were formed by loss of an electron from an OH^- into a neighbouring H^+ ion, thus: $(\text{HO})^-\text{H}^+ + \text{radiation} \longrightarrow \text{HO} + \text{H}$. He further pointed out that the recombination reaction, $\text{H} + \text{OH} \longrightarrow \text{H}_2\text{O}$, would proceed very easily by the Franck-Rabinowitch mechanism, and that the tendency of the hydrogen atom to donate an electron to, and of the hydroxyl radical to accept an electron from, a solute accounted for the oxidising and reducing properties of irradiated water; *e.g.*:

Reduction: $\text{H} \cdot + \text{Ce}^{4+} \longrightarrow \text{Ce}^{3+} + \text{H}^+$; the excess of OH ultimately forming H_2O_2 via molecular oxygen.

Oxidation: $\text{HO} \cdot + \text{Fe}^{2+} \longrightarrow \text{Fe}^{3+} + \text{OH}^-$; the excess of H ultimately forming H_2 .

It is now realised that these simple ideas require considerable modification, and the picture of the primary act which is in best accord with the data may be summarised as follows. Transfer of energy from the fast charged particles to the water molecules which they encounter will produce the following effects.

(1) *Ionisation* of the water molecules. The principal ions so formed are likely to be H_2O^+ (which rapidly reacts to form H^+ aq. + OH with considerable energy release), H^+ (and the associated OH radical), OH^+ (and the associated H atom). These will be distributed along the track with a concentration proportional to the specific ionisation. Since the radical ion will probably react rapidly with neighbouring water molecules according to $\text{HO}^+ + (\text{H}_2\text{O})_n \longrightarrow \text{H}^+\text{aq.} + 2\text{OH}$, the net instantaneous effect will be of a column of small cross-section containing predominantly OH radicals with a few H atoms. Some of the hydroxyl radicals may be electronically excited ($^2\Sigma$) and both species may have excess of translational or internal energy. Such translationally non-average entities will be referred to as "hot," because their effective temperatures will be above normal. The ejected secondary electrons may have considerable energy which will be lost in ionisation and other processes. On the average, such electrons will travel considerable distances before their speeds are reduced to a value which permits capture by the only species present in quantity with appreciable electron affinity, namely, water molecules. H_2O^- ions will thus be formed over a much wider area and in lower concentration than are the positive ions. This difference in concentration will be the more marked the heavier the ionising particle. Since H_2O^- ions break down on hydration, $\text{H}_2\text{O}^- \longrightarrow \text{OH}^- \text{aq.} + \text{H}$, the total effective action of the ionisation processes is formation of $\text{H} + \text{OH}$ in somewhat uneven concentration, but both entities will occur in increasing concentration as the end of the track is approached.¹³¹

¹³⁷ See *Ann. Reports*, 1947, **44**, 60.

¹³⁸ *Nature*, 1944, **158**, 748.

(2) *Excitation.* Both the primary particle and secondary electrons excite some of the water molecules with which they collide. If 33 ev. is the total energy required to create an ion-pair, possibly 12—14 ev. may be used in excitation only. Part may be used to excite vibrations in the "micro-icebergs." The slowness of the degradation of this internal energy to heat is manifested in the "lag" in contraction after the radiation source is removed from pure water.⁷² Much of the 12—14 ev. may be employed in direct dissociation of water molecules, *i.e.*, $\text{H}_2\text{O} \longrightarrow \text{H}(^1\text{S}) + \text{OH}(^2\Sigma \text{ or } ^2\Pi)$.

The overall effect is thus $\text{H}_2\text{O} \rightsquigarrow \text{H} + \text{OH}$, but it is improbable that any appreciable amount is formed by direct electron transfer.

(b) *Secondary Processes.* (1) *Decomposition of water.* Diffusion of radicals and atoms will occur within the tracks, and also from the tracks. The latter process will lead to intermingling of radicals and atoms originating from different tracks. It is important to know whether such a diffusion process follows the normal mechanism in liquids, and therefore whether the diffusion coefficient can be regarded as of the same order of magnitude as that of known molecules of comparable size through water, or whether it occurs by a more rapid process. The possibility of a Grothuss-type transport of H or OH through a water polymer unit, *i.e.*, $\text{HO} + \text{H}(\text{H}_2\text{O})_n\text{OH} \longrightarrow (\text{H}_2\text{O})_{n+1} + \text{OH}$, cannot be overlooked. Experiments on the degree of enrichment of oxygen gas evolved from a dilute solution of hydrogen peroxide in water which is several-fold enriched in H_2^{18}O indicate that the exchange reaction, $\text{H}^{16}\text{O} + \text{H}_2^{18}\text{O} \longrightarrow \text{H}_2^{16}\text{O} + \text{H}^{18}\text{O}$, is not unduly fast.¹³⁹ It would therefore appear that in respect of the OH radical, at least, diffusion from the tracks occurs by normal processes. Competing with the diffusion are the "combination" and "recombination" reactions. The latter is the reaction, $\text{H} + \text{OH} \longrightarrow \text{H}_2\text{O}$, and may concern a hydrogen atom and a hydroxyl radical formed from different water molecules situated some distance from the point of recombination. It is unlikely to require an energy of activation and probably occurs at every collision. On the other hand, the recombining radicals may be derived from the same water molecule, recombination occurring within the solvent "cage" in which they were formed.⁷⁰ Both types of recombination are exothermic and will provide the means by which much of the energy of the radiation is converted into heat. The important difference between the two is that the radicals recombining by the former mechanism will have appreciable separate existences between formation and destruction and may therefore be regarded as more available for reaction with any solute added or produced. By "combination" reactions we denote reaction between like species, namely, 2H or 2OH , the products of which are H_2 and H_2O_2 , respectively.⁷¹ Such products will accumulate most rapidly where the local concentration of the appropriate radicals is highest and the concentration of the other species lowest. Thus, H_2O_2 will be formed in the centre of the track and H_2 over a wider area, both products appearing in larger amounts as the

¹³⁹ E. Collinson and F. S. Dainton, unpublished.

end of the track is approached, and both probably derived from the "ionisational" rather than from the "activational" hydrogen atoms and hydroxyl radicals, since the latter type is better placed for recombination. Furthermore, the lower the energy and the higher the mass of the particulate radiation, the more favourable are the conditions for formation of hydrogen peroxide and hydrogen, a result which has been well established.⁷¹ It has been argued that dipole repulsion forces cause reactions between hydroxyl radicals to require an energy of activation,¹⁴⁰ and some experimental support exists for this.¹⁴¹ The fact that the yield of hydrogen peroxide in de-aerated water decomposed by α -rays is independent of temperature¹¹⁷ shows either that this is not true, or that the radicals are in possession of the necessary energy of activation. The latter suggestion is in keeping with the notion that the radicals are "hot."⁷¹ The sharp decrease of ionic yield on freezing could be due to the polymolecular structure of ice which might increase the temporary "trapping," followed by delayed unproductive release, of a greater proportion of energy than in liquid water.

The presence of dissolved oxygen enhances the yield of hydrogen peroxide owing to the fact that some of the hydrogen atoms react readily according to $H + O_2 \longrightarrow HO_2$, the hydroperoxide radical so formed being subsequently converted into hydrogen peroxide. This mechanism is responsible for most of the yield of hydrogen peroxide in X -irradiated aerated water, and, since this yield increases with rise of temperature, one of these steps must require appreciable energy of activation. This might be the dismutation, $2HO_2 \longrightarrow H_2O_2 + O_2$.

As the concentrations of dissolved products build up during an irradiation, they will diffuse from the tracks and become increasingly liable to attack by those hydrogen atoms and hydroxyl radicals which have appreciable lifetimes before recombination. Possible reactions which are known to occur with great facility at room temperature are (i) $OH + H_2 \longrightarrow H_2O + H$, (ii) $OH + H_2O_2 \longrightarrow HO_2 + H_2O$, and (iii) $H + H_2O_2 \longrightarrow H_2O + OH$; together with (iv) $HO_2 + H_2O_2 \longrightarrow H_2O + OH + O_2$ and (v) $H + O_2 \longrightarrow HO_2$, these provide for a net back reaction, $H_2 + H_2O_2 \longrightarrow 2H_2O$, which will be a chain process. If a solute is present which reacts with one or both of the radicals with great facility, but which, owing to the very high local concentration of "ionisation" radicals formed with massive radiation, cannot gain access to these before combination, then, as Allen suggested,⁷¹ the back reaction will be inhibited and the equilibrium displaced towards the products. This author has argued that such a displacement effect is to be expected from all solutes, not only from those which react with both radicals, *e.g.*, vinyl compounds and hydrolysable solutes, but also from those which react with either the H or OH only. The reason is that prolonged irradiation will establish a balance between oxidised and reduced forms of the solute, the position of the equilibrium

¹⁴⁰ J. Weiss, *Trans. Faraday Soc.*, 1940, **36**, 856.

¹⁴¹ D. E. Lea, *ibid.*, 1949, **45**, 81.

being determined by the standard redox potential. Thereafter, both H and OH will be equally destroyed, and the back reaction suppressed. On the other hand, if high-energy γ -rays are used, very few radicals will be formed in the immediate neighbourhood of similar radicals and a very reactive solute present in sufficient concentration might destroy practically all the radicals, ionisational as well as activational, before combination occurred. The forward reaction would then also be suppressed and no hydrogen peroxide or hydrogen be detected. Much more work requires to be done on this aspect and the more puzzling "gas phase volume" effect described by Allen.

(2) *The chemical nature of indirect action in water.* Solutes may undergo chemical transformation by one, or a combination, of the following mechanisms: (i) photochemical change due to absorption by the solute of part of the Cerenkov radiation; (ii) excitation of the solute when it deactivates excited water polymers; (iii) reaction with hydrogen peroxide or hydrogen; and (iv) reaction with hydrogen atoms or hydroxyl radicals formed in the primary act. These mechanisms are arranged in order of increasing importance. Although process (i) must occur, the fraction of the total reaction effected in this manner is probably very slight. The second mechanism may be operative, since it is known that even low concentrations of ferrous sulphate destroy the "lag" in energy dissipation, but the magnitude of the effect is unknown.⁷² The hydroxyl radical and the hydrogen atom may be regarded as very reactive forms of hydrogen peroxide and hydrogen, respectively, and it is therefore surprising that it is necessary to include mechanism (iii) in addition to (iv). The most direct experimental evidence as to the mode of reaction in any particular system is obtained from studies of the reactivity of the solute to hydrogen, hydrogen peroxide, hydrogen atoms, and hydroxyl radicals separately in the absence of any ionising radiation.

For this purpose reliable methods of generating hydroxyl radicals and hydrogen atoms in water are required. Hydroxyl radicals can be produced (i) by the action of light of wave-length less than 3700 Å. on dilute aqueous solution of hydrogen peroxide, $\text{H}_2\text{O}_2 + h\nu \longrightarrow 2\text{OH}^\cdot$, (ii) by spontaneous or photochemical electron transfer from a powerful oxidising ion to a water molecule of its solvation sheath, e.g., $\text{Co}^{+++} \text{aq.} \longrightarrow \text{Co}^{++} \text{aq.} + \text{H}^\cdot + \text{OH}^\cdot$, or $\text{Fe}^{+++} \text{aq.} + h\nu \longrightarrow \text{Fe}^{++} \text{aq.} + \text{H}^\cdot + \text{OH}^\cdot$, (iii) electron transfer to hydrogen peroxide, e.g., $\text{Fe}^{++} \text{aq.} + \text{H}_2\text{O}_2 \longrightarrow \text{Fe}^{+++} \text{aq.} + \text{OH}^- + \text{OH}^\cdot$, or (iv) oxidation of a strongly reducing ion by dissolved oxygen, e.g., $\text{V}^{++} \text{aq.} + \text{O}_2 \longrightarrow \text{VO}^{+} \text{aq.} + 2\text{OH}^\cdot$. Methods which employ hydrogen peroxide have the marked advantage that, in the absence of a solute, the hydroxyl radical initiates a chain decomposition of the peroxide and much oxygen is evolved. Inhibition, by a solute, of this oxygen evolution is easily detected and can be used as a criterion of reaction of the substrate with the hydroxyl radical. Method (ii) involves cations of high valency, and the presence of strong acid is often necessary to prevent hydrolysis. Method (iv) is particularly valuable for effecting polymeris-

ation of water-soluble vinyl compounds, since the oxygen which is normally an embarrassment owing to its capacity to cause induction periods is, in this case, effectively removed in the initiating reaction and can never exert its retarding action.¹⁴²

In principle, hydrogen atoms could be generated by any process leading to acceptance of an electron by water. This requires a powerful electron donor. A uniform concentration of hydrogen atoms might conceivably be achieved by using a highly reducing ion, aqueous solutions of which spontaneously evolve hydrogen, *e.g.*, U^{3+} .^{*} Alternatively, photochemical stimulation of the electron transfer can be effected, and this method possesses the advantage that the rate is not markedly temperature-dependent and high local concentrations of hydrogen atoms can be produced. Such advantages may be offset if the electron-affinity spectrum of the conjugate oxidising ion falls in the same spectral region or if the solute forms a complex with the ion.¹⁴² Moreover, the solutes which may be used are restricted to those which are either transparent in the appropriate wave-length region or are unaffected chemically by light in this region.

Molecular hydrogen is rarely an effective reducing agent for aqueous solutes, and most oxidising solutes are therefore considered to react with the hydrogen atoms. This may be a simple electron transfer, *e.g.*, $\text{Fe}^{+++}\text{aq.} + \text{H} \longrightarrow \text{Fe}^{++}\text{aq.} + \text{H}^+\text{aq.}$, or addition, *e.g.*, reduction of oxygen or methylene blue,¹⁴³ or opening double bonds,²⁷ or a combination of the two, *e.g.*, $\text{S}_2\text{O}_8^{2-} + \text{H} \longrightarrow \text{HSO}_4^- + \text{SO}_4^-$. It has been demonstrated that acrylonitrile is polymerised and gas evolution prevented when aqueous solutions of slightly acidified ferrous sulphate containing this substance are illuminated with ultra-violet light.¹⁴⁴ Part of the γ - and X-ray-induced polymerisation of this monomer in aqueous solution may therefore be attributed to the hydrogen atoms. Another chain reaction which is probably partly initiated by hydrogen atoms is the radiolysis of hydrogen peroxide solutions.¹⁴⁵

Most reducing solutes which react with hydrogen peroxide will also react with hydroxyl radicals, but the converse does not necessarily hold. Radiochemical reactions in which hydroxyl radicals are presumed to play a part include single-electron-transfer oxidation of reducing ions, *e.g.*, $\text{Fe}^{++}\text{aq.} + \text{OH} \longrightarrow \text{Fe}^{+++}\text{aq.} + \text{OH}^-\text{aq.}$, hydrogen-atom extraction, *e.g.*, $\text{H}_2\text{S} + 2\text{OH} \longrightarrow 2\text{H}_2\text{O} + \text{S}$,¹⁴⁶ and $\text{C}_6\text{H}_6\text{aq.} + \text{OH} \longrightarrow \text{H}_2\text{O} + 0.5\text{Ph}_2$,¹⁴⁷ hydroxylation of aromatic nuclei, *e.g.*, $\text{C}_6\text{H}_6 \longrightarrow \text{C}_6\text{H}_5\cdot\text{OH}$,¹⁴⁷ and initiation of polymerisation.²⁷ In the last two examples, the hydroxyl

¹⁴² D. G. L. James and F. S. Dainton, unpublished.

¹⁴³ Colwell, *Lancet*, 1932, I, 932.

¹⁴⁴ F. S. Dainton, unpublished; M. G. Evans, private communication.

¹⁴⁵ H. Fricke, *J. Chem. Physics*, 1935, 3, 364.

¹⁴⁶ J. Loiseleur, *Compt. rend.*, 1942, 215, 536.

¹⁴⁷ J. Weiss and G. Stein, *Nature*, 1947, 161, 650.

^{*} Added in proof, March 27th, 1949. A wide range of these ions has now been investigated.¹⁴² None appears to fulfil this requirement.

group is readily detected in the reaction products. Most of these reactions would be expected to require little energy of activation; and in keeping with this it is found that temperature has no effect on the rate of oxidation of ferrous sulphate solutions by X- and γ -rays.¹³⁵

Solutes which are of biological importance present certain interesting chemical features. The chemical changes undergone are often not understood, but are associated with a drastic alteration of biological activity which is made the basis of assay. The methods available for identifying the active agent are thus reduced. Two examples must suffice. The enzyme ribonuclease is inactivated by X-rays in dilute aqueous solution. Protection against such inactivation may be achieved by addition of organic reducing agents, e.g., thiol-containing compounds, an observation which suggests that hydroxyl radicals or hydrogen peroxide rather than hydrogen atoms or molecules are responsible. The enzyme is, however, fairly stable to 0.01N-H₂O₂, and it is concluded that hydroxyl radicals must cause the inactivation. E. Collinson, F. S. Dainton, and (Mrs.) B. Holmes¹⁴⁸ have confirmed this directly by demonstrating that ribonuclease is inactivated, and inhibits the evolution of oxygen, when dilute hydrogen peroxide is illuminated by ultra-violet light. By contrast with this behaviour T. Alper¹³⁵ has shown that hydrogen peroxide and not the hydroxyl radical is the active agent in the X-ray inactivation of bacteriophage S.13, since (a) hydrogen peroxide is detected, (b) phage is inactivated by hydrogen peroxide, (c) the amount inactivated, plotted against time, shows a lag to be expected of a series of consecutive steps, and (d) the reaction has a considerable temperature coefficient.

(3) *The kinetics of indirect action.* Several independent attempts have been made which agree in general outlook, but differ in detail, to predict the dependence of ionic yield on such variables as concentration, specific ionisation, etc.¹⁴⁹ All these treatments omit any consideration of the back reaction, an omission which is of less importance when solutes are present which react easily with both hydrogen atoms and hydroxyl radicals. The following over-simplified treatment enables the important features to be emphasised. Let I be the dose rate (ev./W absorbed per unit volume per unit time), and $k/2$ be the net number of water molecules dissociated per W ev. absorbed after allowance has been made for the almost instantaneous recombination of radicals by the Franck-Rabinowitch mechanism. Denote the concentration of any solutes by s^i , s^{ii} , etc., and let k_1' , k_1'' , etc., be the rate constants for removal of the radicals by the appropriate solutes. Thus

$$dn/dt = 0.5kI - \Sigma k_1' s^n - (k_3 + k_4)n^2 \quad . \quad . \quad . \quad (2)$$

where n represents the concentration of radicals, and is initially non-uniform throughout the system, k_3 is the velocity constant for recombination of unlike radicals which have been formed from different molecules, and k_4

¹⁴⁸ Unpublished.

¹⁴⁹ D. E. Lea, ref. 4, Chapter II; Weiss, *Trans. Faraday Soc.*, 1947, **43**, 314; Dainton and N. Miller, *XIth Internat. Congress*, 1947; F. S. Dainton.⁷⁸

is the velocity constant for combination of like radicals in pairs to form hydrogen or hydrogen peroxide. Actually, the extent of mutual interaction of the radicals (the last term) will depend upon the specific ionisation of the tracks, the distribution of hydrogen atoms and hydroxyl radicals within the tracks, and their diffusion constants. The alternative, more quantitative approach⁴ is concerned much more with the fractional number of radicals which have recombined at any instant in a track of given specific ionisation.

If p_1' , p_1'' , etc., are the probabilities that in the radical-solute collision the solute is destroyed, the rate of reaction $= -\Sigma ds'/dt = \Sigma p_1'k_1's'n$, and the ionic yield $M/N = \frac{\Sigma p_1'k_1's' \cdot n}{I}$. When only a single solute is present, two extreme cases are possible :

(a) $k_1's' \gg (k_3 + k_4)n$, whence $M/N = p_1'k/2$

(b) $k_1's' \ll (k_3 + k_4)n$, whence $M/N = p_1'k_1's'[k/2I(k_3 + k_4)]^{\frac{1}{2}}$

Thus at high concentrations the ionic yield is independent of solute concentration and dose rate, whereas at low concentrations the ionic yield decreases with decreasing solute concentration and increasing dose rate. The value of s' at which the dependence of ionic yield on s' commences will be determined by the relative values of k_1' , and $(k_3 + k_4)$. Very reactive solutes will show type-(a) behaviour to lower concentrations than do less reactive solutes, and use of "heavy" radiations which give large specific ionisations will lead to change from type (a) to type (b) at higher concentrations than "light" radiation. Several experiments have been reported for which the dependence of ionic yield on s' and type of radiation can be explained in this way,^{73, 131} and N. Miller³⁷ has shown that change of dose rate has no effect on M/N in region (a) for the oxidation of ferrous sulphate solution.

When the product of the reaction removes the radicals as efficiently as the reactant, it is easily shown that, if no combination of radicals is occurring [type (a)], then $s = s_0 \exp. \left(-\frac{p_1'k_1'}{2s_0} It \right)$. Such exponential decrease of solute concentration with dose (It) has often been observed.¹³³

Protection of one solute (s^I) by a second (s^{II}) is easily seen from equation (2), since the ionic yield with respect to s^I is given by

$$(M/N)' = p_1'kk_1's/2(k_1's' + k_1''s'')$$

Application of this equation enables the relative protection efficiencies of various agents with reference to a given substrate to be assessed.¹³⁴

The above discussion relates to solutes which react with hydrogen atoms or hydroxyl radicals. For those rare cases in which the solute may be inert thereto but reactive to hydrogen peroxide, we have three simultaneous equations :

$$\begin{aligned} \frac{dn}{dt} &= 0.5kI - (k_3 + k_4)n^2 \\ \frac{d(H_2O_2)}{dt} &= k_4n^2 - \Sigma k_5'(H_2O_2)s' \\ - \frac{ds'}{dt} &= p_1'k_5's'(H_2O_2) \end{aligned}$$

There will therefore be a lag phase before the hydrogen peroxide concentration reaches a stationary value, when the rate will be given by

$$-\frac{ds'}{dt} = \frac{p_1'k_5's'k_4kI}{2(k_3 + k_4) \cdot \Sigma k_5}s'$$

Under appropriate conditions, protective action and exponential dependence on dose would be observed, but in no case would the *steady state ionic yield* depend on dose rate. The velocity constant k_5 refers to reaction between the solute and hydrogen peroxide and is likely to have a much larger energy of activation than any rate constant hitherto mentioned. Greater temperature dependence is therefore to be expected for reaction *via* hydrogen peroxide than *via* hydrogen atoms or hydroxyl radicals.¹³⁵

I am grateful to Messrs. E. Collinson and P. Smith for unstinted help in searching the literature.

F. S. D.

2. STRUCTURE OF AQUEOUS SOLUTIONS OF SOAP-LIKE SUBSTANCES.

A soap is an alkali-metal salt of a straight-chain fatty acid or mixture of fatty acids having upwards of about 10 carbon atoms. On grounds of relative availability from natural sources and solubility in the desired temperature range, the most frequent mean numbers of carbon atoms are 12, 16, and 18 in the saturated series and 18 (oleic acid is the *cis*-form) in the series with one double bond in the chain.

Numerous compounds of similar physical properties have become industrially available in recent years, differing in the nature of the ionic group. Many of these have been the subject of extensive academic investigations, and, where the ionic group has been derived from a strong acid or base and is not bulky or complex in structure, these compounds are similar in their behaviour and better suited to exact enquiry, the complications introduced by the hydrolysis of the salts of the weak carboxylic acids being avoided.

These compounds, too, have been placed by some authors under the generic title of "soaps", while in other quarters and largely influenced by trade policy, the extension of this title beyond its original meaning has been vigorously opposed. The general title "paraffin-chain salts" proposed by the Reporter has been very widely used, but suffers from a potentially excessive generality which is becoming increasingly important. With the development of synthetic compounds in this field, particularly products of the petroleum industry, the simple pattern of an unbranched aliphatic chain with a simple *terminal* ionic group is frequently discarded, sometimes through accident of easier synthesis, more often deliberately in order to obtain certain desirable physical properties. Compounds with more than one chain, or branched chains, or containing mixed aliphatic and aromatic elements form solutions of markedly different structure.

We shall therefore distinguish in this Report between normal paraffin-chain salts, including soaps, where the paraffin chain is unbranched and the ionic group terminal (*i.e.*, normal in the sense in which normal primary amyl alcohol is distinguished from secondary and *iso*-alcohols), and complex paraffin-chain salts of various types. The deviation from the simple type is, of course, frequently so small as to leave the most important physical properties largely unaltered.

The industrial development of these compounds as emulsifying, wetting, and suspending agents has sought amongst other objects that of avoiding the limitations of the true soaps due to the very low solubility of their calcium and magnesium salts. This is not simply avoided by replacement of the carboxylic by the sulphonic group, as is sometimes loosely stated, since many of the sulphonates form equally insoluble salts with these metals. It is unfortunate that the alkaline-earth metals are the most intractable in this respect. Soluble paraffin-chain salts of zinc, copper, and even iron are more numerous (even the fatty acids have soluble cuprammonium salts).

More generally resistant to hard water are the "reversed" salts, *i.e.*, those with a surface-active cation. These do not appear to have a corresponding tendency to form insoluble salts with bivalent anions. Most resistant of all are the numerous compounds where the ionic group has been replaced by a non-ionic water-attractive group such as lightly polymerised glycerol or ethylene oxide. These neutral amphiphathic agents have now a very considerable field of technical application. They have, however, been the least studied of the whole group by academic research workers, mainly on account of the great difficulty of obtaining them in a pure state.

Academic work on this group of compounds is still primarily concerned with the nature of their aqueous solutions, and in this report we shall deal with this subject almost exclusively. It is desirable to note, however, that some of the most important technical applications of the compounds have very little relation to the more peculiar features of solution structure since these appear in concentrations well above the range of most technical interest. It is a matter of regret that academic research has seemed here unduly slow to discover a field of at least equal intellectual interest and more technical importance. One may note also that few of the more complex types of salt have found their way into academic literature. Where they have done so, technical preparations have most often been used and too little help seems to have been given by the preparative chemist to his physical colleague—a state of affairs which could be remedied by more preparative activity on the part of the latter.

The present subject came under review in these Reports in 1936¹ and again in 1940.² The Reporter published a summarising article dealing with his own theory of the structure of aqueous solutions of the normal salts in 1939.³ In this article we shall therefore consider fully only the work

¹ N. K. Adam, *Ann. Reports*, 1936, **33**, 103.

² A. S. C. Lawrence, *ibid.*, 1940, **37**, 99. ³ G. S. Hartley, *Kolloid-Z.*, 1939, **88**, 22.

which has appeared since these dates, except where reference to specific earlier papers is necessary for an understanding of the more recent developments. There have been developments along three main branches of the subject: (1) examination, mainly by already established methods, of the more complex salts, (2) study of the solvent power of aqueous solutions, and (3) application of X-ray diffraction technique to the problem.

1. The Behaviour of the More Complex Salts.

It was inevitable that the development of synthetic imitations of soap would lead to that of amphipathic substances of more complex type which, while retaining the essential combination of a non-polar part of the molecule with a strongly water-attracting part, altered substantially the geometrical distribution. Leaving aside the mixed aryl alkyl salts developed technically as wetting agents and the complicated and impure sulphation products of unsaturated glycerides (*e.g.*, Turkey-red oil), the earliest reference to work on compounds of defined structure differing essentially geometrically from the normal paraffin-chain salts appears to be one⁴ in which salts with branched paraffin chains were noted to have remarkable powers of killing acid-fast bacteria. Unfortunately, in this work numerous salts and acids were compared under conditions of undefined differences of physical form, some being undoubtedly in solution and others equally certainly existing as suspensions of more or less crystalline solids.

Reference to aliphatic compounds where the chain is branched from the carbon atom adjacent to the ionic group was first made in the patent literature⁵ in describing the compounds now known as Tergitols, the emulsifying properties of which were later described in the technical literature.⁶ These are sulphates of secondary alcohols where the ionic group is nearer the middle than the end of the chain and where the chain itself may be branched. Later,⁷ the Aerosols were announced. These are sulphonates of dialkyl esters of succinic acid, the sulphur being attached to one of the middle carbon atoms of the acid. Here, too, the ionic group is near the middle of the chain, but, since the ester groups also will contribute in smaller measure to the water attraction, they are perhaps better regarded as compounds where two chains of moderate length are attached to one ionic head in place of the traditional single long chain of the soaps and earlier synthetic detergents. A convenient series of compounds of this type was made by the Reporter⁸ by sulphonation of various dialkyl ethers of dihydric phenols.

It was expected that these compounds would be able less easily to form the normal type of dilute solution micelle than compounds containing the same number of aliphatic carbon atoms in a single chain. The Reporter

⁴ W. M. Stanley, G. H. Colman, C. M. Greer, J. Sacks, and R. Adams, *J. Pharm. Exp. Ther.*, 1932, **45**, 121.

⁵ B.P. 440,539.

⁶ B. G. Wilkes and J. N. Wickert, *Ind. Eng. Chem.*, 1937, **29**, 1234.

⁷ B.P. 446,568.

⁸ G. S. Hartley, *J.*, 1939, 1828.

has advanced in a number of papers⁹ the view that the micelles which form in dilute solutions of the normal paraffin-chain salts are essentially liquid and approximately spherical, their radius being determined by the depth to which the end of a paraffin chain can reach when its ionic end group is anchored approximately in the surface. Replacement of one long by two short chains must reduce the maximum radius of this type of micelle and therefore very greatly reduce the number of ions in each micelle. As a result, the surface of the micelle will be much less completely hydrophilic, and surface energy considerations³ would lead us to the conclusion that the micelle will be much less readily formed.

On the other hand, an ion with two short chains will not be adsorbed on a macroscopic oil surface in water with much less energy advantage than an ion with a single chain of the same total length. At a concentration where no aggregates exist in either solution we might expect the single-chain salt to be more surface active than the double-chain salt. At higher concentrations, however, where micelles have formed in the aqueous solution of the single-chain salt, the concentration of separate ions will be much higher in the double-chain salts. The surface activity of the latter will therefore become greater. In a study of the interfacial tensions between carbon tetrachloride and *cyclohexane* and solutions of various compounds of the ether series above mentioned,¹⁰ it was indeed found that the double-chain salts, while less active than a single-chain salt in very dilute solutions, cause the interfacial tensions to fall much lower in higher concentrations. At a concentration of 0.08% the monosulphonate of the dioctyl ether of resorcinol was found to have an interfacial tension against a mixture of the above non-polar liquids of only 0.04 dyne/cm. Only experimental difficulties of measurement prevented lower interfacial tensions being recorded. Normal paraffin-chain salts do not reduce interfacial tension to less than 1 dyne/cm. in any concentration.

It was noted in the above work that these salts are not so effective with aromatic oils, and a drift of interfacial tension with time was evident owing presumably to slow transfer of salt to the oil phase. These salts are all much more soluble in organic liquids than comparable normal salts. Copper and nickel salts of Aerosol O.T., for example (O.T. is the sulphonate of the dioctyl ester of succinic acid), are obtained by evaporation as clear glasses which are indefinitely soluble in most organic liquids.¹¹ The potassium salt of 1 : 3-dioctyloxybenzene-4-sulphonic acid is freely soluble in benzene and chloroform, moderately in petrol, but almost insoluble in dry acetone. That of 1 : 4-dioctyloxybenzene-3-sulphonic acid is very soluble in all solvents with the exception of paraffins at one extreme and water at the other.^{8, 11} It is to be expected that these salts would, on geometrical grounds, form less stable crystals and so be universally more soluble, but this does not seem a fully satisfactory explanation. One might also expect a greater facility in the formation in organic solvents

⁹ Summarised in ref. 3.

¹⁰ G. S. Hartley, *Trans. Faraday Soc.*, 1941, **37**, 130.

¹¹ *Idem*, unpublished observations.

of the reversed type of micelle, considered ² to be present in solutions of alkali and alkali-earth soaps in non-polar oils. This would lead to the expectation of greater solubility in paraffins than in more polar solvents, which is not found to be general. More work on these almost absurd solubilities would be desirable.

It is well known that the soaps give rise successively to three new liquid phases as the concentration is increased.¹² No phase-rule studies on the more complex salts seem to have been made, but it is evident to anyone who has worked with these substances that here too new phases can arise and in much lower total concentrations. At ordinary temperatures the sulphonates of near-symmetrical dialkyl ethers of resorcinol have a limited range of concentration in which clear homogeneous solutions are obtained. Above this concentration a very fine emulsion is formed which can be coagulated by simple salts to give a macroscopic second liquid phase. The Reporter ⁸ has noted that crystals of potassium 1 : 3-dioctyloxybenzene-4-sulphonate, formed by slow evaporation of an aqueous glycerol solution, disperse spontaneously to the emulsion form if transferred to water.

The crystals mentioned above are massive rhombohedra, obviously of fundamentally different structure from the very thin plates formed by the normal salts. Yet another unexpected property of these double-chain salts is their ability to form stable thin films in aqueous and glycerol solutions. These surpass in length of life the standard ammonium oleate solution,⁸ but have evidently lower viscosity as they thin down by drainage through the coloured interference bands to the very thin black film much more rapidly than do soap solutions and remain almost indefinitely in the black state when protected from evaporation and dust. P. A. Winsor ¹³ has observed that this thinning gives a characteristic ghost-like appearance to a "head" of froth in these solutions (he worked with near-symmetrical secondary sulphate esters) and that the normal salts are antagonistic to this type of film. Addition of a small concentration of a normal salt produces a solution with very transient frothing power. Further addition replaces the stable ghost froth by a stable opaque froth similar to that formed by soap solutions.

A. W. Ralston and his collaborators ¹⁴ have applied the established conductivity technique to study the aggregation of solutions of these double-chain salts. They examined a series of dimethyldialkylammonium salts. They found here, too, the rather abrupt fall of equivalent conductivity at a critical concentration, known to indicate the sudden formation of aggregates in the normal salts. The fall was, however, not so great and the critical concentration not so low as in a solution of a normal salt with the same

¹² See, e.g., J. W. McBain and M. C. Field, *J. Physical Chem.*, 1926, **30**, 1545; J. W. McBain, L. H. Lazarus, and A. V. Pitter, *Z. physikal. Chem.*, 1930, **A**, **147**, 87; J. W. McBain and E. Gonick, *J. Amer. Chem. Soc.*, 1946, **68**, 683.

¹³ *Nature*, 1946, **157**, 660.

¹⁴ A. W. Ralston, D. N. Eggenberger, and P. L. du Brow, *J. Amer. Chem. Soc.*, 1948, **70**, 977.

number of aliphatic carbon atoms. For example, the critical concentrations for C_8C_8CC and $C_{10}C_{10}CC$ compounds are about $0.03N$ and $0.0025N$ as compared with interpolated values of about $0.002N$ and $0.0004N$ for the isomeric $C_{15}CCC$ and $C_{19}CCC$ compounds. It is noteworthy that the discrepancy is much greater between the salts of lower molecular weight. No great difference was found between the $C_8C_{12}CC$ and $C_{10}C_{10}CC$ compounds.

Extensive solubility work recently published by P. A. Winsor, which will be referred to in other connections below, includes measurements of the critical concentration¹⁵ in a series of sodium sulphates of *n*-tetradecane, differing in the position of the carbon atom to which the sulphate group is attached. The indicator method of M. L. Corrin, H. B. Klevens, and W. D. Harkins¹⁶ was employed. It was found that the critical concentration rose throughout the series from that of the normal compound, $1.7 \times 10^{-3}N$, to that of the most symmetrical (7-sulphate), $16 \times 10^{-3}N$. Consistently with H. V. Tartar's observations, however, the relative change for a displacement of one carbon atom is least when the compound is near symmetrical.

J. W. McBain¹⁷ and his collaborators have measured the freezing points in low concentrations of aqueous solutions of some of the double- and branched-chain salts. They find a less abrupt fall of osmotic coefficient at a less well-defined critical concentration than in normal salts, that for Aerosol O.T., $0.003N$, being some ten times greater than for a normal salt with 18 aliphatic carbon atoms. For Aerosol I.B. (*diisobutyl*) the critical concentration is about $0.3N$. The ratio is consistent with the findings of A. W. Ralston and his collaborators¹⁴ for the dimethyldialkylamines.

H. V. Tartar and his collaborators have reported some very precise conductivity data on aqueous solutions of alkylbenzenesulphonates¹⁸ and alkyltrimethylammonium bromides¹⁹ over a range of temperatures. The extreme sharpness of the break in the curves relating equivalent conductivity to the square root of the concentration is very clearly demonstrated in this work. In the sulphonates the sulphonic group was *para* to the alkyl and, in this arrangement, it was concluded that the benzene ring was the equivalent of one and a half aliphatic carbon atoms in its effect on the critical concentration. From the same laboratory was published an interesting study²⁰ of conductivity in another type of double-chain salt, where both cation and anion have one short paraffin chain, in this case trimethyloctylammonium octylsulphonate. The critical concentration was much lower and the fall much greater than in the case where one ion is simple.

Another development in conductivity studies may conveniently be reported here. E. C. Evers and C. A. Kraus²¹ noted that octadecylpyrid-

¹⁵ *Trans. Faraday Soc.*, 1948, **44**, 467. ¹⁶ *J. Chem. Physics*, 1946, **14**, 480.

¹⁷ J. W. McBain and O. E. A. Bolman, *J. Physical Chem.*, 1943, **47**, 94; J. W. McBain and A. P. Brady, *J. Amer. Chem. Soc.*, 1943, **65**, 2072.

¹⁸ A. B. Scott and H. V. Tartar, *ibid.*, p. 692.

¹⁹ R. G. Paquette, E. C. Lingafelter, and H. V. Tartar, *ibid.*, p. 686.

²⁰ A. B. Scott, H. V. Tartar, and E. C. Lingafelter, *ibid.*, p. 698.

²¹ *Ibid.*, 1948, **70**, 3049.

inium iodate behaves unusually in that the equivalent conductivity first rises abruptly over a short range with increase of concentration above the critical, before going through a maximum and then falling steeply in the normal manner. The nitrate and bromide showed normal behaviour throughout. One may note that the mobility of the paraffin-chain ion constituent always rises at the critical concentration,²² as would be expected from the reduced resistance of the combined ions. The fall of total conductivity is due to the predominant effect of the secondary association of ions of opposite sign when the charge density is increased by the primary aggregation. Could homo-ionic aggregation occur in an infinitely dilute solution, a rise of total equivalent conductivity would always be expected. The more dilute the solution in which primary aggregation can occur and the smaller the conductivity of the counter ions, the more likely is this phenomenon to occur. It is not therefore surprising that it is not evident until at least 18 carbon atoms are introduced into the single chain and then only with less mobile counter ions. A conductivity rising with aggregation was, of course, first foretold by J. W. McBain, although, in the case of very much higher concentrations where a rising conductivity was first found, we now know that the explanation must be sought on different lines.²³ It was first found experimentally by C. Robinson and H. E. Garrett²⁴ in the case of certain dyes. At high field strengths the same type of curve was found²⁵ in cetylpyridinium chloride, the effect of secondary aggregation being reduced at high relative velocities of the ions.

In a later paper, P. F. Grieger and C. A. Kraus²⁶ first confirm earlier results of A. F. H. Ward²⁷ that addition of lower alcohols blurs the critical phenomenon and, in sufficient concentration, eliminates it, but they find additionally that, with some salts, the presence of 10–35% of methyl alcohol in the aqueous solvent calls into being, at the critical concentration, a transient rise of equivalent conductivity, which is not evident in water alone. This is found with octadecylpyridinium chloride, bromate, and formate but not with bromide, nitrate, and oxalate. This peculiar behaviour remains obscure.

The transient rise of equivalent conductivity at the critical concentration in water alone and in normal field strengths was also found by A. W. Ralston *et al.*¹⁵ in the double-chain quaternary salts when two 12-carbon-atom chains were present. In this case we have altogether 26 aliphatic carbon atoms, probably a higher number than in any compound previously known to be soluble at ordinary temperatures. The critical concentration is about $10^{-4}N$ and the micelle will presumably contain fewer ions than a normal salt aggregating at this concentration, so that the conditions are very favourable to an abnormally small effect of secondary ionic association.

²² C. S. Samis and G. S. Hartley, *Trans. Faraday Soc.*, 1938, **34**, 1288.

²³ Ref. 3, p. 36.

²⁴ *Trans. Faraday Soc.*, 1939, **35**, 771.

²⁵ J. Malsch and G. S. Hartley, *Z. physikal. Chem.*, 1934, **A**, **170**, 321.

²⁶ *J. Amer. Chem. Soc.*, 1948, **70**, 3803. ²⁷ *Proc. Roy. Soc.*, 1940, **A**, 512.

Solubility measurements in solutions of more complex salts will be reported in the next section.

2. Solubility Phenomena.

Many organic substances of limited solubility in water are rendered completely miscible by addition of paraffin-chain salts. Others, of very low solubility in water, are much more soluble in solutions of paraffin-chain salts. This phenomenon is concerned with a reversible, equilibrium process and is quite distinct from that of emulsification. Benzene, for example, can be added slowly to a 10% solution of cetylpyridinium chloride in water and is taken up entirely therein to give an optically empty solution, provided the benzene concentration does not exceed about 7%, depending on temperature. Further added benzene forms a visible emulsion containing droplets of varying size where average size depends on the history of the mixture. Several careful researches²⁸ have established the reversible equilibrium in the true solutions. For hexane in sodium oleate solution, J. W. McBain and J. J. O'Connor²⁹ have measured the equilibrium vapour pressure in solutions below saturation and find a normal type of pressure-composition curve.

There has been a general usage of a new word to describe this phenomenon, namely, "solubilisation". The Reporter considers that this is unnecessarily confusing. It appears to imply that an essentially new process is under investigation and it is often held, in consequence, that the resulting solutions are not in equilibrium. We are not dealing with an entirely new process when we dissolve benzene in an aqueous paraffin-chain salt solution. The peculiarity is that the solvent is unusual in structure rather than that the solute is brought into an unusual state. Phenomenologically, the difference between a system where alcohol or acetone is the co-solvent and one where a paraffin-chain salt is the co-solvent is quantitative only.

A much smaller amount of a paraffin-chain salt than of acetone is necessary to bring amyl alcohol and water into complete miscibility. A much larger amount of naphthalene is dissolved by a given concentration of paraffin-chain salt in water than by the same concentration of acetone in water. There is, associated with this difference, an even more distinctive one, but still essentially quantitative. A rapidly increasing additional amount of naphthalene is brought into solution by each successive equal increment of acetone. With paraffin-chain salts, over a considerable range of concentration, the additional concentration of saturant is proportional to the additional concentration of co-solvent. The solvent power of the paraffin-chain salt, unlike that of the acetone, is not appreciably lost by dilution with water. Below the concentration known from other measurements to be the critical one for formation of micelles, the solvent power is, however, very rapidly lost.

²⁸ R. S. Stearns, H. Oppenheimer, E. Simon, and W. D. Harkins, *J. Chem. Physics*, 1947, **15**, 496; J. W. McBain and A. A. Green, *J. Amer. Chem. Soc.*, 1946, **68**, 1731.

²⁹ *Ibid.*, 1940, **62**, 2855.

The fundamental explanation of this difference is now generally agreed by all workers in this field. The unusually high solvent power of the paraffin-chain salts, but little affected by dilution, is due to the salt being present in the form of relatively large aggregates. Amicroscopically, the co-solvent is not diluted by the water and thus retains its solvent power. The solvent power of ordinary co-solvents is also due to aggregates, but these are relatively smaller and therefore less effective and widely distributed in size and therefore the mean size is much dependent on concentration. The less ideally miscible with water is the co-solvent, the less completely does it lose its solvent power, as is well illustrated in the data for naphthalene and the three lowest alcohols obtained by J. Christiansen³⁰ and previously commented on in the present connection by the Reporter.³¹

It is noteworthy that there are observations, somewhat neglected in this connection, of the solubility of several organic substances of low water solubility in solutions of simpler organic electrolytes, such as sodium benzoate and salicylate.³² The normal salting-out effect of the electrolyte is reversed at quite low concentrations and in high concentrations the "organic" effect predominates. There is, of course, no sharply defined critical concentration, and the solvent power, presumably due to small clusters as in solutions of alcohol in water, is great only in concentrated solutions.

The Reporter³¹ found that the solubility of azobenzene in aqueous solutions of cetylpyridinium chloride is approximately the same as in an equivalent amount of hexadecane. His argument that the micelle is therefore essentially liquid in its paraffinic interior has received adverse comment³³ when taken out of its context. Simple paraffinic solvent properties are only to be expected and are only found when the solute is non-polar. Polar, and especially amphipathic, molecules are likely to be oriented in the surface of the aggregate. Since the diameter of the latter is only of molecular dimensions, it is to be expected that orientation will have a very great effect on solubility. Many simple dyes are much more soluble³³ in paraffin-chain salt solutions than would be expected on simple addition of the water and paraffin solvents. J. W. McBain and H. McHan³⁴ have shown that dimethyl phthalate, which has practically zero solubility in water and a low solubility in higher paraffins, is much more soluble in paraffin-chain salt micelles.

Recently, W. D. Harkins and H. Oppenheimer³⁵ have proposed a distinction between "solubilisation" when the solute is dissolved in the interior of the micelle and "penetration" when it is oriented in its structure.

³⁰ *Medd. K. Vetenskapsakad. Nobel-Inst.*, 1918, **4**, No. 2.

³¹ G. S. Hartley, *J.*, 1938, 1968.

³² J. Traube, I. Schöning, and L. J. Weber, *Ber.*, 1927, **60**, 1808; E. Lersson, *Z. physikal. Chem.*, 1930, **A**, **148**, 304; 1931, **A**, **153**, 299, 466; H. Freundlich and G. V. Slottman, *Biochem. Z.*, 1927, **188**, 101.

³³ J. W. McBain, article on "Solubilisation" in *Advances in Colloid Science* (Interscience, 1942), Vol. 1.

³⁴ *J. Amer. Chem. Soc.*, 1948, **70**, 3838.

³⁵ *J. Chem. Physics*, 1948, **16**, 1000.

There can be no doubt that molecules themselves amphipathic will be incorporated in the micelle with similar orientation. A. F. H. Ward²⁷ considers that the lower alcohols are held predominantly in the micelle surface. E. Angelescu and T. Manolescu³⁶ consider phenols to be similarly disposed or even oriented outside the micelles.

I. M. Kolthoff and W. F. Johnson³⁷ have made use of the solvent power of micelles for dimethylaminoazobenzene to determine the critical concentrations in several soaps. They found the critical concentration very indefinite with rosinate. J. W. McBain, R. C. Merrill, and J. R. Vinograd³⁸ find that the solubility of phenylazo- β -naphthylamine in soap solutions is considerably less than in solutions of salts of paraffin-chain cations and of many more complex salts. R. C. Merrill³³ finds a less marked disadvantage of the soaps as solvents for *o*-tolylazo- β -naphthol, and A. M. Soldate's results³³ put potassium oleate as much less effective than Aerosol O.T. as a solvent for propylene vapour.

In the studies just referred to, Turkey-red oil, which is, of course, largely sulphated unhydrolysed glycerides, stands out as having solvent power for the dyes examined comparable with that of the higher alkyl quaternary ammonium salts. The bile salts have no very outstanding solvent power in solution, the extraordinary adsorption properties of deoxycholic acid in the solid state evidently being due to an abnormal crystal structure. In solutions of Aerosol O.T. and sodium deoxycholate the critical transition from the ultimately dissolved state to the aggregated state is shown by the solubility measurements to be less abrupt than with normal paraffin-chain salts, consistently with the other evidence quoted above on the former compound and related dialkyl salts.

The phenomenon of indicator equilibrium displacement, noted in 1934³⁹ and later applied to quantitative titration of paraffin-chain cations by paraffin-chain anions⁴⁰ and to investigation of the ratio of surface to bulk pH,⁴¹ has been the subject of further research and experimental refinement. It is, of course, an example of the "solubilisation" phenomenon. M. L. Corrin and W. D. Harkins⁴² have found indicators particularly suitable to the determination of the critical concentration without interference with it. Other less direct applications of solvent power have been made in analytical procedure.⁴³ The influence of the solvent properties of the paraffin-chain salt micelle on the bactericidal effect of dissolved phenols has been the subject of a recent research.⁴⁴

Phenols and alcohols of medium molecular weight have long been used

³⁶ *Kolloid-Z.*, 1941, **94**, 319.

³⁷ *J. Physical Chem.*, 1946, **50**, 440.

³⁸ *J. Amer. Chem.*, 1941, **63**, 670.

³⁹ G. S. Hartley, *Trans. Faraday Soc.*, 1934, **30**, 444.

⁴⁰ G. S. Hartley and D. F. Runnicles, *Proc. Roy. Soc.*, 1938, **A**, **168**, 420.

⁴¹ G. S. Hartley and J. W. Roe, *Trans. Faraday Soc.*, 1940, **36**, 101.

⁴² *J. Amer. Chem. Soc.*, 1947, **69**, 679.

⁴³ T. U. Marron and J. Schifferli, *Ind. Eng. Chem. Anal.*, 1946, **18**, 49.

⁴⁴ A. E. Alexander and A. J. H. Tomlinson, Faraday Society Discussion, "Recent Advances in Surface Chemistry" (in the press).

technically in the formulation of special soap solutions and studies of soap-water-phenol systems were among the first made in this field.⁴⁵ Renewed interest has recently been taken in similar systems. J. H. Schulman and T. S. McRoberts⁴⁶ have examined the consolution of water and benzene or paraffin by sodium oleate in the presence of various alcohols, by titrating mixtures to the end-point of fluid transparency. Accepting at that time the lamellar view of the micelle in aqueous solutions, they consider that the penetration into it of the oil phase first liquefies it and that the swollen micelle is then capable of growth to spherical droplets of the order of 200 \AA . diameter. Whether an oil-continuous or water-continuous system results they explain in terms of the relative wettability by water or oil of the interfacial layer consisting of alcohol and soap molecules. Distinction between these two types of system is made experimentally by conductivity observations. They find that, over certain ranges of composition, the systems are, with regard to this inversion, extremely sensitive to the molecular size of the alcohol and the nature of the hydrocarbon.

R. C. Pink⁴⁷ has examined the equilibrium adsorption of water vapour by benzene solutions of ethanolamine oleate and finds that the adsorption increases very rapidly with further rise of temperature above about 45° . This he attributes to a fusion of a previously crystalline aggregate—in this case, of course, of the “reversed” structure, with the paraffin tails arranged exteriorily.

A very extensive study has been made by P. A. Winsor of oil, alcohol or amine, water, paraffin-chain salt systems. Various types of system can be realised,⁴⁸ isotropic solutions from oil-continuous to water-continuous, such solutions in equilibrium with excess oil or water, and anisotropic gel systems at intermediate compositions between the two extreme types. He interprets the behaviour in terms of a somewhat ill-defined ratio of the interaction between the amphipathic substance and oil to that between the amphipathic substance and water. This somewhat obscures the geometrical factor in the amphipathic or, as this author prefers, “amphiphilic”, property. This is brought out in the section dealing with all seven *n*-tetradecane sodium sulphates,¹⁶ where, as previously mentioned, it is shown that the critical concentration for micelles in aqueous solution increases as the ionic group moves towards the centre of the chain, which would indicate on this author's view an increasing water attraction, and yet the compounds behave as though more oil-attractive as far as solubilisation is concerned. The author apparently goes to an opposite extreme to that visited by explorers with the X-ray diffraction camera, in that he minimises the importance of organised structure, although accepting the anisotropic gel phase as a lamellar intermediate between the amicro-emulsions of oil-in-water and water-in-oil forms envisaged by J. H. Schulman.⁴⁶

In the other papers in this series, P. A. Winsor notes that the addition

⁴⁵ E. Angelescu and M. Popescu, *Kolloid-Z.*, 1930, **51**, 336.

⁴⁶ *Trans. Faraday Soc.*, 1946, **42**, B, 165.

⁴⁷ *Ibid.*, p. 170.

⁴⁸ *Ibid.*, 1948, **44**, 376.

of simple salts⁴⁹ can in part replace the addition of intermediate alcohols by increasing the ratio of oil-phase attraction to water-phase attraction of the amphipathic substance. The effects of the nature of the oil phase⁵⁰ and of that of the amphipathic substance⁵¹ are examined, the latter supplementing earlier work by R. Durand⁵² on sodium soaps from C_2 to C_{11} . Solubilisation in glycol in place of water is also examined⁵³ and is distinguished by absence of the anisotropic gel phases. The author considers that the hydrogen-bonded pseudo-ice structure in water is necessary for the adhesion between the units of dispersed phase without which gel structure cannot be evident.

3. Organisation in Concentrated Solutions.

The discovery in 1937⁵⁴ of the production by clear solutions of soaps of an X-ray diffraction pattern of a much more definite nature than that produced by normal liquid systems threw new light on the problem of the structure of these solutions. Unfortunately, the X-ray diffraction camera as a precision tool is held in rather uncritical respect by many physical chemists unfamiliar with the complications of the subject, and specialists in the subject have been perhaps insufficiently familiar with other work on solutions of soap-like substances to have appreciated that there might be some doubt about apparently obvious conclusions from the measurements. The result has been that the advance following on this discovery has been much more rapid measured as a scalar than as a vector quantity.

The diffraction patterns indicate the presence of a single characteristic short spacing of about 4.6 Å. and a long spacing, greater than twice the length of the extended paraffin-chain ion, which increases with dilution. The diffraction ring due to the long spacing is not detectable at concentrations of salt much under 10%, but that due to the short spacing is still evident at less than 5%.^{55, 56}

J. Stauff examined the sodium salt of the C_{14} primary sulphate ester in parallel experiments at temperatures of 20°, where the salt exists as a suspension of microscopic curd fibres, and at 75°, where it is in clear solution. In the curd condition, two rings due to short spacings are evident and one due to a long spacing which in this condition of the salt is, as expected, independent of concentration. The values are 4.55, 4.00, and 38.2 Å. In solution the first two fuse together to a single constant value of 4.60 and the second ranges from about 62 Å. at 20% concentration of salt to 42 Å. at 80%.

Following K. Hess and J. Gundermann⁵⁴ and H. Kiessig and W. Philip-

⁴⁹ *Trans. Faraday Soc.*, 1946, **42**, B, 382.

⁵⁰ *Ibid.*, p. 387.

⁵¹ *Ibid.*, p. 390.

⁵² *Compt. rend.*, 1946, **223**, 898.

⁵³ P. A. Winsor, *Trans. Faraday Soc.*, 1948, **44**, 451.

⁵⁴ K. Hess and J. Gundermann, *Ber.*, 1937, **70**, 1800.

⁵⁵ J. Stauff, *Kolloid-Z.*, 1939, **89**, 224.

⁵⁶ W. D. Harkins, R. W. Mattoon, and M. L. Corrin, *J. Amer. Chem. Soc.*, 1946, **68**, 220.

poiff,⁵⁷ Stauff interprets the short spacing as that between adjacent parallel planes in which the chains lie parallel to one another, and the replacement of the two corresponding identity periods in the crystalline phase by a single period as indicating that, during the transition of the curd suspension to clear solution, partial fusion of the crystal occurs similar to that in transition from a normal crystal to a smectic melt. In the crystal, all the zigzag C-C links of a chain are in the same plane and these planes are regularly disposed with respect to one another. In the smectic state these chain planes, by virtue of freedom to rotate, have effectively become cylinders. It will be noted that this process involves a lateral expansion amounting to some 15% on the original area, only some 5% of which is attributable to thermal expansion alone.

All these and other^{58, 59} investigators have, until very recently, accepted the interpretation of the long spacing by Hess, Kiessig, and their collaborators.^{54, 57} It is considered to have a similar origin to the constant long spacing in the true crystal, which represents, of course, the distance between planes containing the terminal ionic groups, which planes are nearly perpendicular to the chains. The expansion of this spacing with dilution of the salt is considered to be due to the increasing separation of the pairs of ionic planes by a more or less organised layer of water. The general picture is that of an assembly of smectic-crystalline leaflets, the so-called laminar micelles, separated by layers of water of thickness characteristic of the dilution.

This concept may perhaps have been suggested by analogy with the qualitatively similar behaviour of montmorillonite clays on hydration.⁶⁰ In this well-established case, however, a water layer thickness of more than 4 molecules has never been observed, whereas the laminar soap micelles must be separated by up to a maximum of at least 8 water molecules. Moreover, the clays remain insoluble. Any excess water produces a suspension of macroscopic particles of size determined by the origin and treatment of the clay and separated to distances determined by sedimentation conditions.

This picture of regularly separated laminæ has frequently been described and equally frequently drawn. It has the merit of being easily drawn. The difficulty is to stop drawing it, and one may fairly ask whether Nature would not find a corresponding difficulty. There is no doubt at all that the clear solutions of paraffin-chain salts are equilibrium systems in the strict sense, and no hysteresis of any exactly measurable property has yet been detected. Addition of further paraffin-chain ions to any one of these pictures of the laminar micelle would seem to involve no difference from

⁵⁷ *Naturwiss.*, 1939, **27**, 593; see also K. Hess, W. Philippoff, and H. Kiessig, *Kolloid-Z.*, 1939, **88**, 40.

⁵⁸ P. Krishnamurti, *Indian J. Physics*, 1929, **3**, 307.

⁵⁹ D. Dervichian and F. Lachampt, *Bull. Soc. chim.*, 1945, **12**, 189.

⁶⁰ See E. A. Hauser and L. S. Le Beau in Alexander's "Colloid Chemistry" (Reinhold, 1946), Vol. 6, p. 191.

the last additions in any way which could distinguish the chosen size as being energetically or statistically preferable. Only when clusters of molecules are very small will there be any optimum size in an equilibrium system unless some special factors operate to give the optimum size a strongly marked maximum potential energy loss for each molecule entering the cluster.

Criticism along these lines has already been made in advance by K. H. Meyer and A. van der Wyk⁶¹ directed against the Reporter's hypothesis of an optimum size of micelle on the mistaken assumption that the micelle considered had a parallel alignment of ions. It has been answered by the Reporter elsewhere^{40, 3} for the case of the spherical micelle, but remains a very valid objection to the laminar micelle. In developing a theory of a reversible aggregation colloid it is just as important to find a mechanism for the limitation of aggregation as it is to find a primary cause of aggregation. The argument is therefore of some importance and it has been so consistently overlooked that it is desirably briefly to repeat it. Aggregation of paraffin-chain ions is due to the very strong mutual attraction of water molecules which tend to eliminate as far as possible the intrusion of indifferent paraffin between them. The strong attraction between water and the ionic end groups is responsible for limiting this process of extrusion of the separate chains into clusters presenting a much smaller area of paraffin to the water. If the arrangement is laminar, however, this would explain only a limitation of the thickness of the micelles and leave their area indeterminate. If the greater entropy of the liquid arrangement of the paraffin chains causes this state to be preferred (and where it does not do so we have in fact indefinite laminae, *i.e.*, our salt is insoluble), then a spherical cluster will result, the single linear dimension of which is now controlled by the balance of forces referred to. If the spherical micelle were much smaller than necessary to enable a fully extended chain to penetrate from its surface to the centre, a greater area of paraffin than necessary would be exposed to the water. If it were much larger, then ionic groups would have to leave the water against the strong attraction of the latter, or the assembly would have to deviate from spherical form and so the entropy would be reduced. It is perhaps desirable to recall that a strongly marked optimum size of micelle, varying but little with concentration of paraffin chain or added salts, is an experimental fact.⁴⁰

A similar difficulty about the laminar micelle theory was raised by J. D. Bernal in the Faraday Society Discussion on Swelling and Shrinking in comment on the contribution by D. G. Dervichian.⁶² He pointed out that a simple calculation showed that the increase of spacing between alternate ionic planes, if assumed to be due to entry of water between neighbouring planes, could account only for a fraction of the total water present. To take an example from J. Stauff's data⁵⁵ on the C₁₄ sodium

⁶¹ *Helv. Chim. Acta*, 1937, **20**, 1321.

⁶² *Trans. Faraday Soc.*, 1946, **42**, B, 180.

sulphate, in a system containing 40% of water, the long spacing has increased from its "dry" value of 38 Å. to 48 Å. This will account for 16% only of the water. The remaining 24% must separate the indefinite lamellæ laterally, where it will be in contact with the exposed sides of the parallel bundles of paraffin chains.

Before considering the latest developments in this subject, mention must be made of a further quantitative difficulty in the lamellar hypothesis, pointed out by W. D. Harkins, R. W. Mattoon, and M. L. Corrin⁶³ after following up, in a more extensive investigation, Kiessig and Philippoff's observation⁵⁷ that the long spacing is increased by dissolving ("solubilising") oils in the soap solution. They consider that the oil is located as another layer, this time between the planes defined by the terminal methyl groups. The difficulty here is the reverse of that found in accounting for the water volume, in that oil increases the spacing by much more than would be expected from its inclusion in this location without other changes in the system. The authors are therefore forced to the view that the introduction of the oil layer has a secondary effect, by some unknown mechanism, on the water layer.

In a later paper, Harkins *et al.*⁶⁴ report the results of more thorough investigation of the X-ray diffraction photographs which reveal a new, less well-defined, long spacing attributed to the individual thickness of the micelle. At this stage they favour a cylindrical micelle with the paraffin chains parallel to the cylinder axis. They envisage the interpretation of the original long spacing on a point lattice system in which "no special shape for the micelle is necessary". In this paper the diffusion-measurement evidence⁴⁰ for the size of the micelle is for the first time considered in relation to the X-ray studies. The cylindrical model has been further considered by them.⁶⁵

M. L. Corrin has recently briefly reviewed the X-ray diffraction evidence from the point of view of the spherical micelle hypothesis, and finds the two not inconsistent. He considers that "the observed patterns can arise from a system of spherical micelles and that the Bragg law 'spacings' may be meaningless". The communication is too brief to permit the derivation of the distance distribution functions which he proposes, and a fuller treatment by this author will be awaited with interest.

The Reporter had already suggested⁶⁶ that a distortion of the spherical micelles might occur, owing to packing effects operating in the concentrated solutions examined by the X-ray technique. Such effects were not considered in the development of the theory³ of spherical micelles from evidence based only on measurements in dilute solution. It now appears unnecessary to envisage such distortion. It would presumably give rise to a more rather than a less complex diffraction picture. Once the principle is admitted

⁶³ *J. Colloid Sci.*, 1946, **1**, 105.

⁶⁴ R. W. Mattoon, R. S. Stearns, and W. D. Harkins, *J. Chem. Physics*, 1947, **15**, 209.

⁶⁵ *Idem*, *ibid.*, 1948, **16**, 156.

⁶⁶ G. S. Hartley, *Trans. Faraday Soc.*, 1946, **42**, B, 6.

that the corresponding, regularly spaced assemblies of atoms responsible for the diffraction need not be planes, the spherical micelle offers much the simplest explanation of the diffraction phenomena. In a recent contribution ⁶⁷ the Reporter has suggested that the strong electrostatic repulsion between the micelles will, in concentrated solution, cause them to be more or less regularly disposed and in such a way that each is the maximum distance from the maximum number of neighbours. This condition is satisfied by the three dimensional "honey-comb" or close-packed assembly, the geometry of which leads directly to the simple relationship

$$l = (3\phi/2\sqrt{2}\pi)^{1/3}r$$

where l is the distance between centres of neighbouring spheres, r their radius, and ϕ the fraction of the total volume occupied by the spheres. It is shown, not only that this equation leads to a good approximation to the observed variation of l (the "long spacing") with ϕ on the assumption of constant r , but that the calculated values of r are, as expected and as found by diffusion measurements, slightly greater than the length of a fully extended chain.

Not only is the water thus accounted for, but this view of the structure explains also the anomaly of a disproportionately great increase of l on addition of oils. A non-polar oil will be contained mainly in the interior of the micelle and tend to be concentrated near its centre, so that a maximum increase of radius results from the addition of a small amount of oil. In the extreme case, let the oil be located exclusively at the centre, occupying a sphere of radius δ . The whole micelle now has radius $r + \delta$, and the paraffin chains occupy the volume $\frac{4}{3}\pi[(r + \delta)^3 - \delta^3]$. The volume ratio of added oil to paraffin chains is thus, in the limit of $\delta \rightarrow 0$, equal to $\delta^2/3r^2$. The relative increment of r resulting from addition of an amount of oil corresponding to a small fraction f of the paraffin-chain volume will thus be $\sqrt{3f}$, whereas the relative increment of spacing in the simple laminar model will be equal to f . A disproportionate increase of l follows directly from that of r .

J. H. Schulman and D. P. Riley ⁶⁸ have published an investigation by X-ray diffraction technique of the transparent emulsion systems previously described by the former.⁴⁶ They interpret their results in terms of the lattice point distances of the emulsion droplets, and the investigation shows how far this simple view is applicable. They find evidence of the distortion which must occur when the ratio of dispersed phase exceeds the 74% corresponding to close packing of equal spheres. These authors issue a caution against the full acceptance of their model for the case of solutions of the paraffin-chain salts alone on the ground that an ideally liquid spherical micelle would not show the characteristic short spacing found in photographs of these solutions. It is to meet this difficulty that Harkins *et al.* propose a micelle with a cylindrical, parallel-packed core rounded off at

⁶⁷ *Nature*, in the press.

⁶⁸ *J. Colloid Sci.*, 1948, **3**, 383.

the sides with more randomly-packed chains presenting their ionic groups to the water.

The short spacing cannot be due to regular disposition of ionic groups on the outside of the micelle. Diffusion measurements⁴⁰ indicate an effective radius for the cetylpyridinium micelle of about 25 Å. This will contain between 70 and 100 paraffin-chain ions. The mean distance apart of the ionic groups will therefore be not less than 8.5 Å. The outer diffraction band probably arises from a regular spacing between paraffin chains. No exact comparison seems to have been made with the pattern produced by a liquid paraffin of comparable chain length, to see whether the true liquid in bulk has sufficient regions of ordered arrays to make any further explanation necessary.

It has been mentioned above that the soaps, and perhaps other salts of paraffin-chain anions, have less solvent power than those of paraffin-chain cations. The long spacings also appear to be greater in the latter, indicating a larger micelle.⁶³ It is a question worthy of further study, by all methods available, whether there may be more internal order in the anionic micelles.

That the spherical liquid micelle is not a complete explanation of all the properties of paraffin-chain salt solutions has always been appreciated by the Reporter. Although many solutions, even when concentrated, have viscosities little in excess of that of water, yet others may be very viscous or gelatinous over a limited range of temperatures or even show a permanent elasticity persisting to very low concentrations.⁶⁰ The latter effect is very specifically influenced even by the nature of the small ions. The occurrence of pronounced elasticity in very dilute solutions indicates that, in these cases, very stable filamentous particles must be present. One may imagine that an indefinitely long cylindrical form of the paraffin micelle is preferred in these cases, with the paraffin chains parallel to the axis, as in Harkins's model,⁶⁵ but adhering together by the ionic lattices, which would account at once for a specific ion effect. On the other hand, the chains might be as chaotically disposed as is geometrically possible, with the ionic groups on the cylindrical surface, an arrangement which we should expect to be more probable in view of the factors causing limited aggregation of amphipathic ions. A filamentous arrangement is suggestively similar to the "myelinic figures" described by D. G. Dervichian.⁶² The very high degree of elasticity shown suggests that the filaments must be elastically contractile. The liquid cylinder would have this property, since it would be extensible without disruption and its surface would tend to contract to the smallest area consistent with the radius not exceeding the effective stretched length of the chain ion.

Optical anisotropy has been a much neglected method of enquiry into this subject. Its occurrence in streaming suspensions of soap curd is, of course, well known, as also the strong birefringence of the gelatinous phases formed in many systems where organic liquids are present within certain

⁶⁰ G. S. Hartley, *Nature*, 1938, **142**, 161.

concentration limits⁴⁸ and at sufficiently high concentrations of the pure salts.⁷⁰ The ordinary solutions should also show streaming birefringence if the micelle were indeed of laminar form.

In the course of pioneer studies of the aggregation of lower fatty acids and soaps which revealed the existence of the critical transition from ultimately dissolved to aggregated solution, J. Grindley and C. R. Bury⁷¹ studied the changes in a number of physical properties, including that of density. They found that aggregation resulted in a decrease of the partial volume of water and an increase in that of the solute. The importance of this fact has not been generally recognised. The Reporter⁶⁶ has drawn attention to the fact that the expansion of the salt may be so great as to give rise to an increase in the volume of the whole system, water plus crystalline salt, when solution occurs. Since the partial volume of a simple electrolyte is always smaller than its volume in the solid state, the expansion of the paraffin-chain salt must be due to increase of volume of the paraffinic portion, which would, of course, be expected on transition of the organised crystal lattice to a liquid arrangement.

Density measurements on solutions of the higher paraffin-chain salts are not sufficiently exact and comprehensive to enable a precise estimate of the density of the paraffinic portion of the micelle to be made. Taking the data at 25° for potassium salts,⁷² we find that the differences of partial molal volumes between the octoate and propionate are 79.2 c.c. at 0.3N where no aggregation is evident and 88.9 c.c. at 1.0N where it is effectively complete. The volumes per CH₂ group are 13.2 and 14.8 c.c. Corresponding values derived from the difference between octoate and acetate are 13.1 and 14.5 c.c. per g.-mol. CH₂. The volumes per g.-mol. CH₂ in liquid paraffins obtained from densities of hexane, octane, decane, and hexadecane are fairly constant at about 16.3 c.c.

Scott and Tartar¹⁸ record densities at 25° of the C₁₀, C₁₂, and C₁₆ trimethylammonium bromides from the differences between which we may similarly deduce volumes per g.-mol. CH₂ (average between 0.1 and 0.4N) to be 16.5 c.c.*

The partial volumes even in simple electrolytes, such as potassium acetate, vary considerably with concentration and the significance of density measurements, as well as the provision of more accurate data, is a matter which merits further consideration. There is a *prima facie* case that the interior micelle density in the higher paraffin-chain salts is at least as low as that of the liquid hydrocarbon.

Harkins and his collaborators⁶³ report density measurements on

⁷⁰ J. W. McBain and E. Gonick, *J. Amer. Chem. Soc.*, 1946, **68**, 683.

⁷¹ *J.*, 1929, 679.

⁷² D. G. Davies and C. R. Bury, *J.*, 1930, 2263.

* Professor E. C. Lingafelter has kindly communicated to the Reporter the following density figures at 25°. For the C₄ compound at 0.01N, 1.00046; for C₆ and C₈ compounds at 0.2N, 1.00321 and 1.00160. From these data we obtain the following values for the volumes per g.-mol. of CH₂. From the difference C₁₈-C₈ at 0.2N, 16.25. From the difference C₁₈-C₆ at 0.2N, 16.6. From the difference C₁₈-C₄ at 0.1N, 16.5.

potassium laurate solutions in which *n*-heptane and 1 : 2 : 3-trimethylbutane and ²⁸ ethylbenzene were dissolved. The first and the last liquid have, in the solutions near saturation, apparent densities nearly equal to those in the bulk liquids, but, in very dilute solution of the added liquid, the apparent densities are considerably higher. This might be expected if we consider the micelle, straining to be as large as possible, to be not completely filled in the centre until non-polar molecules are added. 1 : 2 : 3-Trimethylbutane, on the other hand, has an apparent density in dilute solution approximately equal to that in bulk and a *higher* density near saturation. Its bulk density is considerably higher than that of *n*-heptane and any volume change occurring on solution in bulk in normal paraffins would need to be known before speculation on this remarkable result would be profitable.

G. S. H.

3. CHEMICAL KINETICS: HOMOGENEOUS THERMAL GAS REACTIONS.

In his Presidential Address to the Chemical Society, Sir Cyril Hinshelwood ¹ has discussed, in terms of general principle, the present position of chemical kinetics. It has become evident that the overall "reaction order" has not now the theoretical significance which it may once have appeared to possess, however important the concept may still be as a practical tool of the experimenter. Most reactions take place in a series of stages, either as chain processes, involving interactions between free atoms and radicals, or as non-chain reactions, in which, again, each individual step may be of great simplicity.

Correspondingly, there has been, in recent years, great interest in the individual reactions of free atoms and radicals ² and progress in this direction has been reviewed in *Annual Reports*.³ However, these Reports have not, for many years,⁴ reviewed the overall kinetics of gas reactions; and this is the subject of the present Report. In so large a field it is impossible to be exhaustive, so we have deliberately selected reactions (paying some attention to examples which have been important in the history of reaction kinetics)^{5, 6, 7} to illustrate the kind of progress which has been made. In order to concentrate upon overall kinetics, we have had to leave without mention much important work upon elementary reactions, such as that of Steacie ² with hydrogen atoms.

¹ *J.*, 1947, 694.

² *E.g.*, cf. E. W. R. Steacie, "Atomic and Free Radical Reactions," New York, 1946; and Faraday Society Discussion, 1947, **2**, on the "Labile Molecule."

³ Cf. M. Ritchie, *Ann. Reports*, 1940, **37**, 79; C. E. H. Bawn, *ibid.*, 1943, **40**, 36; D. H. Hey, *ibid.*, 1944, **41**, 181; W. A. Waters, *ibid.*, 1945, **42**, 130; J. Weiss, *ibid.*, 1947, **44**, 60.

⁴ Cf. *ibid.*, 1934, **31**, 46; 1935, **32**, 89; 1936, **33**, 86; 1937, **34**, 43.

⁵ Hinshelwood, "Kinetics of Chemical Change in Gaseous Systems," 3rd edn., Oxford, 1934; "The Kinetics of Chemical Change," Oxford, 1940.

⁶ H. J. Schumacher, "Chemische Gasreaktionen," Dresden and Leipzig, 1938.

⁷ R. N. Pease, "Equilibrium and Kinetics of Gas Reactions," Princeton, 1942.

Overall Order of Reaction.

Second-order Reactions.—The formation and decomposition of hydrogen iodide stand out in exhibiting a second order which bears a direct relation to the molecular events which determine reaction. (For newer work on these and the corresponding reactions of deuterium compounds, cf. A. H. Taylor and R. H. Crist.⁸) The fate of other reactions which have, at one time or another, been formally classified as second-order reactions may be illustrated by the example of the thermal decomposition of acetaldehyde.

The thermal decomposition of acetaldehyde. The earlier work upon this reaction has been critically reviewed by Pease;⁷ and the conflicting evidence as to whether the decomposition occurs by a chain mechanism or not has been summarised by J. R. E. Smith and C. N. Hinshelwood,⁹ who have reinvestigated the reaction. Points in favour of a chain mechanism are: (1) Very careful work by M. Letort¹⁰ showed that the order was 1.5, in agreement with the Rice-Herzfeld theory³¹ of chain reactions. (2) The reaction appeared to follow a mechanism similar to that of the photochemical decomposition which was known to involve free radicals.¹¹ (3) The rate was reduced by propylene.¹² (4) Theoretical arguments based on spectroscopy had been advanced to show that internal rearrangement preceding dissociation was unlikely.¹³ (5) The presence of free radicals had been established.¹⁴ On the other hand, there was some evidence against a chain mechanism. (1) Nitric oxide seemed normally not to inhibit the reaction.¹⁵ (2) Too few free radicals appeared to be present.¹⁶ (3) The reaction appeared to be similar to that of the "fully inhibited" decomposition of benzaldehyde.¹⁷ The reaction had been found to exhibit a variable order and the simultaneous occurrence of more than one mechanism had been postulated.¹⁸

Smith and Hinshelwood⁹ find that increasing additions of propylene reduce the rate of decomposition at 550° until a limiting value is reached; further additions of propylene have a slight catalytic effect. They also find that nitric oxide does reduce the reaction rate only at low acetaldehyde pressures; at moderate pressures inhibition is masked by a strong catalytic effect. The reaction proceeding with the limiting rate attained by "full inhibition" with propylene is of approximately second order; and a velocity coefficient calculated for a bimolecular collisional activation involving two square terms agrees well with the observed value (as it does also for formaldehyde). By subtracting the "fully inhibited" from the normal rate,

⁸ *J. Amer. Chem. Soc.*, 1941, **63**, 1377. ⁹ *Proc. Roy. Soc.*, 1942, **A**, **180**, 237.

¹⁰ *J. Chim. physique*, 1937, **34**, 206, 265, 355, 428.

¹¹ A. O. Allen and D. V. Sickman, *J. Amer. Chem. Soc.*, 1934, **56**, 2031.

¹² F. O. Rice and O. L. Polly, *J. Chem. Physics*, 1938, **6**, 273.

¹³ T. W. Davis and M. Burton, *ibid.*, 1939, **7**, 1075.

¹⁴ M. Burton, J. E. Ricci, and T. W. Davis, *J. Amer. Chem. Soc.*, 1940, **62**, 265.

¹⁵ L. A. K. Staveley and C. N. Hinshelwood, *J.*, 1936, 812.

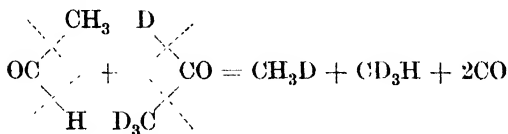
¹⁶ F. Patat and H. Sachsse, *Z. physikal. Chem.*, 1936, **B**, **31**, 105.

¹⁷ R. E. Smith and C. N. Hinshelwood, *Proc. Roy. Soc.*, 1940, **A**, **175**, 131.

¹⁸ C. J. M. Fletcher and C. N. Hinshelwood, *ibid.*, 1933, **A**, **141**, 41.

it is possible to investigate the part of the reaction which may be assumed to be due to a chain mechanism; it appears to be of the first order.

The simultaneous occurrence of a molecular and a chain reaction has been proved in a very satisfactory manner by J. C. Morris,¹⁹ who decomposed mixtures of fully deuterated and ordinary acetaldehyde at 542°. Great pains were taken to purify the materials, and in particular to remove all traces of oxygen, and to reduce the polymerisation of the aldehyde to a minimum. When this careful pretreatment is applied, the decomposition products contain mainly CH₄, CD₄, and CO, and only small amounts of mixed methanes (CH₃D, etc.). The reaction can therefore proceed neither by a chain mechanism (involving CH₃ radicals) nor by a bimolecular process such as



Moreover, the reaction rates observed for the highly purified material approach those of Smith and Hinshelwood's "fully inhibited" reaction and are lower than the rates observed by all other investigators.

On the other hand, when "untreated" mixtures of CH₃·CHO and CD₃·CDO, or mixtures of "pretreated" materials to which small amounts of oxygen had been added, were decomposed, the products contained large amounts of CH₃D, CHD₃, and—surprisingly—CH₂D₂.

Neither prolonged heating of mixtures of CH₄, CD₄, CO, and traces of O₂, nor the decomposition of pure CH₃·CHO in the presence of CD₄ and CO gives rise to the formation of appreciable amounts of mixed methanes.

These results appear to prove (though this is not fully accepted by Steacie²) that the decomposition of pure acetaldehyde proceeds by a unimolecular mechanism, and that the presence of minute amounts of impurities—in particular of oxygen—gives rise to a chain reaction. Morris estimates that "untreated" aldehyde decomposes to the extent of 50% by a chain mechanism. Smith and Hinshelwood's work indicates 60–70% of chain mechanism. The discrepancies between the rates reported for this reaction can be readily understood. Not even Morris's careful treatment succeeded in reducing the chain reaction to below 10–20% of the overall rate. The order of the reaction is still between 1 and 2.

Although this work explains much that has baffled previous investigators, it raises some new problems. The order of the *molecular* reaction remains in doubt. The appearance of appreciable amounts of CH₂D₂ among the products of the *chain decomposition* does not lend support to the chain mechanisms that have been suggested. One may also wonder whether small amounts of oxygen or other impurities are not responsible for the chain mechanism in other reactions where this has not been suspected.

The effect of oxygen on the decomposition of acetaldehyde has been

¹⁹ J. Amer. Chem. Soc., 1944, **66**, 584.

further investigated by M. Letort and N. M. Letort.²⁰ Pure acetaldehyde is thermally stable below 400°, but in the presence of oxygen the rate of decomposition is still measurable at 150°. In mixtures of acetaldehyde (237 mm.) and 0.1—20 mm. of oxygen only definite fractions of aldehyde are decomposed. It is thus possible to calculate the number of molecules decomposed by one molecule of oxygen. This number varies with the temperature in a surprising manner, giving rise to an N-shaped curve. There is a maximum of 200 at 200°, followed by a minimum (65) at 315°, after which the curve rises steeply. The curve obtained by plotting the logarithm of the initial velocity against $1/T$ shows a bend at 190°. It appears that the activation energy is 13 kcal. below 180° but 24 kcal. at 200—290°.

Experiments of E. Leifer and H. C. Urey,²¹ who followed the decomposition of acetaldehyde by means of an interesting, though as yet inaccurate, new mass-spectrographic technique, indicate a second-order reaction.

Free radicals obtained by the pyrolysis of diacetyl strongly catalyse the decomposition of acetaldehyde and other compounds.²² This catalysis is not reduced by the presence of nitric oxide, although in the case of dimethyl ether, the diacetyl-promoted pyrolysis is strongly inhibited by nitric oxide.²³

The decomposition of acetaldehyde is also catalysed by hydrogen sulphide. W. L. Roth and G. K. Rollefson²⁴ found the reaction to be homogeneous. No hydrogen sulphide is consumed by the reaction, and the products are methane and carbon monoxide as for pure acetaldehyde. The overall activation energy is 36 kcal. (the value found by Smith and Hinshelwood in the absence of catalysts is 47 kcal.).

Third-order Reactions.—Interactions of nitric oxide with oxygen and with halogens are the classical third-order reactions,^{5, 6, 7, 34} although these have not always been held to demand a termolecular process as the vital step. However, the reaction of nitric oxide with chlorine is subject to heterogeneous complications;²⁵ and it is not certain that the oxidation of nitric oxide is free from them. In new work on the vexed question of "intensive drying," E. M. Stoddart²⁶ reported non-interaction between oxygen and nitric oxide, intensively dried in separate vessels, but only when mixing of the gases took place in the oxygen-containing bulb. He inferred that heterogeneous processes, influenced by adsorbed moisture, were essential to the oxidation of nitric oxide, contrary to M. Bodenstein's original view. F. B. Brown and R. H. Crist,²⁷ using very carefully purified gases, find the oxidation of nitric oxide to be of third order, at 25°, for 3- and 6-fold variations of reactant concentrations, with pressures of nitric

²⁰ *Compt. rend.*, 1948, **226**, 77.

²¹ *J. Amer. Chem. Soc.*, 1942, **64**, 994.

²² F. O. Rice and W. D. Walters, *ibid.*, 1941, **63**, 1701.

²³ C. H. Klute and W. D. Walters, *ibid.*, 1945, **67**, 550.

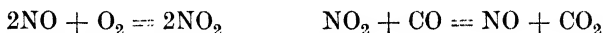
²⁴ *Ibid.*, 1942, **64**, 1707.

²⁵ E. M. Stoddart, *J.*, 1940, 823; 1944, 388.

²⁶ *J.*, 1939, 5.

²⁷ *J. Chem. Physics*, 1941, **9**, 840.

oxide between 0.01 and 0.1 mm. and of oxygen between 8 and 22 mm. The rates observed differ from those of Bodenstein (obtained with about 10 mm. pressure of each reactant) by 5.5%. Brown and Crist²⁷ have also examined the reaction $\text{NO}_2 + \text{CO} = \text{CO}_2 + \text{NO}$ (found to be of second order) at 225–290°; and they have investigated the products and rates of reaction occurring in mixtures of nitric oxide, oxygen, and carbon monoxide at 25–265°. In the ternary mixtures they observe the formation of carbon dioxide at temperatures which are too low for it to be ascribed to the above reaction between carbon monoxide and nitrogen dioxide. Moreover, experiments at higher temperatures,²⁸ with the ternary mixtures of NO, O₂, and CO, gave reaction rates proportional to the first power of the nitric oxide concentration. These two facts are inconsistent with the mechanism



and Brown and Crist propose the reactions



to account for at least part of the third-order oxidation of nitric oxide, together with $\text{NO}_3 + \text{CO} = \text{NO}_2 + \text{CO}_2$ for the ternary mixtures containing carbon monoxide.

Heterogeneous reactions occur in the mixtures containing carbon monoxide; but the above mechanism applies to homogeneous reaction studied in Pyrex glass vessels rinsed with potassium chloride solution.

The oxidation of nitric oxide by nitric acid vapour has been studied.²⁹ The reaction has "some termolecular characteristics" but surface effects are prominent.

First-order Reactions.—The history of these is a curious one. At one time it was argued that unimolecular processes in gases could not result from collisional activation. Then the Lindemann–Hinshelwood theory (subsequently elaborated) showed that they could; and first-order gas reactions were discovered experimentally. A little later these were interpreted by some as chain reactions.³¹ Still more recently, it has been held (cf. R. N. Pease^{7, 32}) that many of the apparently first-order decompositions, which furnish the subject matter for the whole discussion, are, in fact, better represented *experimentally* as reactions of order 1.5.

Dinitrogen pentoxide. One reaction, whose first order has never been denied, is the thermal decomposition of dinitrogen pentoxide vapour,³³ which, indeed, retains its speed and first order down to embarrassingly low

²⁸ G. M. Calhoun and R. H. Crist, *J. Chem. Physics*, 1937, **5**, 301; R. H. Crist and J. E. Wertz, *ibid.*, 1939, **7**, 719.

²⁹ J. H. Smith, *J. Amer. Chem. Soc.*, 1947, **69**, 1741.

³⁰ Cf. H. C. Ramsperger, *Chem. Reviews*, 1932, **10**, 27.

³¹ *E.g.*, F. O. Rice and K. F. Herzfeld, *J. Amer. Chem. Soc.*, 1934, **56**, 284; *J. Chem. Physics*, 1939, **7**, 671; cf. F. O. Rice and E. Teller, *ibid.*, 1938, **6**, 489; A. Kossiakoff and F. O. Rice, *J. Amer. Chem. Soc.*, 1943, **65**, 590.

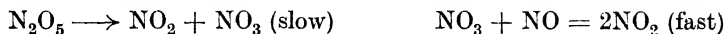
³² *J. Chem. Physics*, 1939, **7**, 749.

³³ *E.g.*, cf. F. Daniels, "Chemical Kinetics," Ithaca, New York, 1938.

pressures (of the order 0.05 mm.). An abnormally large collision diameter was proposed to account for this.³⁴ Doubt has been expressed whether the diminution of speed at even this low pressure is due to the expected theoretical insufficiency of the rate of activation. F. Daniels and P. L. Veltman³⁵ suggested, as a chemical explanation, that the interaction of nitric oxide and dinitrogen pentoxide, assumed to be a rapid step, in both the old and the new mechanism (see below) for the dinitrogen pentoxide decomposition, might, at very low pressures, have a speed comparable with that of the dissociation of N_2O_5 molecules. J. H. Smith and F. Daniels³⁶ find the reaction between dinitrogen pentoxide and nitric oxide, at 0–25°, with reactant pressures from a few hundredths of a mm. up to 20 mm., to be susceptible to catalysis by moisture and surface. The rate of an essentially homogeneous reaction in vessels coated with paraffin is approximately proportional to the pentoxide concentration and nearly independent of nitric oxide concentration, particularly at low pressures of the latter. The overall reaction is proved to be



and the mechanism suggested tentatively is



A new interpretation for the dinitrogen pentoxide decomposition has been suggested by R. A. Ogg,³⁷ who proposes the mechanism

- (1) $N_2O_5 \longrightarrow NO_3 + NO_2$ (k_1)
- (2) $NO_3 + NO_2 = N_2O_5$ (k_2)
- (3) $NO_3 + NO_2 = NO_2 + O_2 + NO$ (k_3)
- (4) $NO + N_2O_5 = 3NO_2$ (rapid)

There being reason to suppose that $k_3 \ll k_2$

$$-d[N_2O_5]/dt = 2d[NO]/dt = 2k_1k_3[N_2O_5]/(k_2 + k_3) \sim (2k_1/k_2)k_3[N_2O_5]$$

The apparent first-order constant is thus a product of an equilibrium constant k_1/k_2 and a bimolecular constant k_3 . The theoretical grounds for anticipating a diminution of order and rate at low pressures therefore vanish.

Pyrolyses of vapours. The theory of unimolecular decompositions was founded upon three main groups of reactions. These were the decompositions of ethers and of azo-compounds³⁰ and certain isomerisation processes. As already mentioned, both the experimental and the theoretical interpretation have been questioned.

Whatever be the theoretical interpretation, it can scarcely be denied that there exist homogeneous gas reactions which are empirically of the

³⁴ L. S. Kassel, "The Kinetics of Homogeneous Gas Reactions," New York, 1932; cf. R. H. Fowler and E. A. Guggenheim, "Statistical Thermodynamics," Cambridge, 1939, p. 525.

³⁵ *J. Chem. Physics*, 1939, **7**, 764.

³⁶ *J. Amer. Chem. Soc.*, 1947, **69**, 1735.

³⁷ *J. Chem. Physics*, 1947, **15**, 337; cf. O. K. Rice, *ibid.*, p. 689.

first order over a limited range of conditions. For example, the decomposition of benzyldeneazine³⁸ at 335° gives first-order velocity coefficients, independent of the initial pressure, in individual experiments; and the time for a given fractional decomposition is constant for initial pressures ranging from 5 mm. ($t_{\frac{1}{2}} = 4.6$ mins.) to 378 mm. ($t_{\frac{1}{2}} = 4.2$ mins.). The discussion turns, however, on reactions observed over wider pressure ranges. According to the theory of unimolecular decompositions, the first-order behaviour prevailing at high pressures may be expected to change over and approach second-order kinetics at sufficiently low pressures. R. N. Pease^{7, 32} has put forward the view that many of the reactions which have been interpreted as unimolecular decompositions are better represented, experimentally, over the *whole range* of pressures as reactions of order 1.5. The best example is the decomposition of diethyl ether. The supposedly first-order velocity coefficients attained at 0.5 atm. pressure have been found to rise further when pressures up to 20 atm. (and later up to 300 atm.) are used (for refs., see Pease⁷). Pease represents the reaction over the whole pressure range as one of order 1.5, with a velocity coefficient constant within a factor of 2. This would correspond to a mechanism of the type: $\text{Et}_2\text{O} \rightarrow \text{R}$; $\text{R} + \text{Et}_2\text{O} \rightarrow \text{products} + \text{R}$; $2\text{R} \rightarrow \text{X}$.

Questioning also the "unimolecular" interpretation of the azomethane decomposition, on the ground that this reaction is chemically far more complex³⁹ than had been supposed, so that pressure measurements are not a safe guide in measuring the reaction velocity, Pease concluded that the isomerisation of *cyclopropane* to propylene was the only reaction to which the theory of unimolecular reactions could properly be applied. In a new investigation of this reaction, E. S. Corner and R. N. Pease⁴⁰ have observed, at 500°, first-order velocity coefficients which do not appear to fall by more than some 8% for initial pressures of 910–150 mm.; but then fall substantially as the initial pressure is reduced to 10 mm. A velocity coefficient derived from a radical mechanism is very satisfactorily constant over the whole initial pressure range. The effects of added gases fail to decide between the "unimolecular decomposition" and "free radical" mechanisms. Nitric oxide, propylene, ethylene, and hydrogen are practically without influence upon the rate of reaction. In the presence of decomposing *n*-butane, the isomerisation is accelerated.

The whole discussion calls for two remarks. (1) As pointed out by Hinshelwood,⁴¹ a chain mechanism, of the type quoted above for ether, itself involves a unimolecular decomposition as one step. (2) The representation of vapour decompositions as processes of order 1.5 is based on the data for reactions whose chain components have not been inhibited by nitric oxide.

Even if the experimental order is accepted as unity, it had earlier been

³⁸ G. Williams and A. S. C. Lawrence, *Proc. Roy. Soc.*, 1936, **A**, 156, 444.

³⁹ E. W. Riblett and L. C. Rubin, *J. Amer. Chem. Soc.*, 1937, **59**, 1537; H. A. Taylor and F. P. Jahn, *J. Chem. Physics*, 1939, **7**, 470.

⁴⁰ *J. Amer. Chem. Soc.*, 1945, **67**, 2067. ⁴¹ *J.*, 1948, 531.

argued,³¹ with supporting experimental evidence, that the reactions were not unimolecular decompositions, but chain reactions, proceeding by mechanisms which happened to give an experimental first order. This question was resolved by the discovery^{5, 42} that chain components in these decompositions could be inhibited by small additions of nitric oxide, which reduced the rate of decomposition to a fraction of its original value, independent of further additions of nitric oxide over a certain range. The residual reaction was taken to be a genuine unimolecular decomposition. Certain reactions appeared to defy retardation by nitric oxide; among them were the decompositions of acetophenone⁴³ (in contrast to that of benzaldehyde¹⁷) and of acetone (and also of ethyl vinyl ether^{43a}). However, J. R. E. Smith and C. N. Hinshelwood⁴⁴ have found the decomposition of acetone to be partially inhibited by propylene¹² and also by nitric oxide, which must be applied in rather larger amounts than usual, indicating a low mean chain length. Both the uninhibited and the residual reactions are of first order at pressures >100 mm. at 570° . (For other recent work on acetone, see Steacie;² also G. M. Harris and Steacie⁴⁵ and V. B. Falkovsky and M. Ya. Kagan.⁴⁶) Rather similar results have been obtained for methyl ethyl ketone.^{46a} Much nitric oxide is needed to produce a small retardation in the initial stages; and the decomposition is thought to be unimolecular. The activation energy of 67.2 kcal. is ascribed to rupture of the methyl-carbonyl bond (cf. $E = 68$ kcal. for the *uninhibited* decomposition of acetone).

It could still be held, however, that the residual reaction was a chain reaction and that nitric oxide could start, as well as stop chains;¹² and identity of reaction products in the decomposition of *n*-butane at 525° ,⁴⁷ in absence and in presence of nitric oxide, has been considered to support this view. It has been countered, however, by J. R. E. Smith and C. N. Hinshelwood,⁹ who find that nitric oxide and propylene reduce the rate of reaction to the same residual value in the decomposition of diethyl ether and also in that of propaldehyde. Moreover, the decomposition of propaldehyde, maximally inhibited by nitric oxide, is not further retarded by propylene. This is strong evidence that the residual reactions are free from chains. With diethyl ether,⁴⁸ the residual reaction is of first order. The products are essentially the same for the normal reaction and for the reaction inhibited by nitric oxide. With propaldehyde and benzaldehyde it is approximately of second order.⁹

Among other instances of inhibitory action by nitric oxide, it has been

⁴² L. A. K. Staveley and C. N. Hinshelwood, *J.*, 1937, 1568.

⁴³ R. E. Smith and C. N. Hinshelwood, *Proc. Roy. Soc.*, 1940, *A*, **176**, 468.

^{43a} S. N. Wang and C. A. Winkler, *Canadian J. Res.*, 1943, *B*, **21**, 97.

⁴⁴ *Proc. Roy. Soc.*, 1945, *A*, **183**, 33.

⁴⁵ *J. Chem. Physics*, 1944, **12**, 554.

⁴⁶ *J. Physical Chem. Russia*, 1948, **22**, 445.

^{46a} C. E. Waring and W. E. Mutter, *J. Amer. Chem. Soc.*, 1948, **70**, 4073.

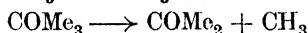
⁴⁷ E. W. R. Steacie and H. O. Folkins, *Canadian J. Res.*, 1940, *B*, **18**, 1.

⁴⁸ J. G. Davoud and C. N. Hinshelwood, *Proc. Roy. Soc.*, 1939, *A*, **171**, 39; 1940, *A*, **174**, 50.

noted that 1% of this causes an extreme lengthening of the induction period preceding the homogeneous dimerisation of acetylene at 400—700°. ⁴⁹ Transient inhibitory action by nitric oxide has been observed in the decomposition of *n*-butane ⁵⁰ and of methyl *n*-butyl ether. ⁵¹ With the latter, cyanide was detected in the reaction products, as in some other reactions inhibited by nitric oxide. It has been suggested ⁵² that, in combining with methyl radicals, nitric oxide forms CH₃·NO, which isomerises to formaldoxime CH₂·NOH. Formaldoxime ⁵² decomposes at 350—415° in a first-order reaction (up to half-life above 400°), primarily to hydrogen cyanide and water. The activation energy of 39 kcal. is close to the N-O bond energy (37.7 kcal.) in alkyl nitrites. ⁵³ With hydrogen atoms, nitric oxide may form HNO. ⁵⁴ Formaldoxime has actually been isolated in the products of interaction of nitric oxide with free radicals from decomposing di-*tert.*-butyl peroxide. ⁵⁸ The value 6.5 kcal. has been estimated for the activation energy of interaction of nitric oxide with methyl radicals. ⁵⁵ The "inhibition curves" describing the influence of inhibitor concentration upon the extent of inhibition (which are, for example, independent of diethyl ether pressure for nitric oxide, but not for propylene) provide information about the action of inhibitors. ^{9, 44, 56} It is inferred that propylene, when compared with nitric oxide, combines more readily with CH₃ than with larger radicals, such as CH₂·O·C₃H₅ or CH₂·CO·CH₃.

Recent work upon thermal decompositions, not mentioned in the publications of Schumacher ⁶ and of Steacie, ² includes the following.

The decomposition of di-*tert.*-alkyl peroxides ⁵⁷ in the vapour phase follows the mechanism



The kinetics have been investigated. ⁵⁸ At 140—160°, the decomposition of di-*tert.*-butyl peroxide is a first-order homogeneous reaction. The rate of decomposition is not reduced (as judged from flow experiments) by propylene or nitric oxide, although, as mentioned above, the latter combines with methyl radicals formed in the second stage of the reaction. There is no chain reaction. The energy of activation is 39.1 kcal. The O-O bond

⁴⁹ D. A. Frank-Kamenetsky, *Acta Physicochem. U.R.S.S.*, 1943, **18**, 148; E. A. Blumberg and D. A. Frank-Kamenetsky, *J. Physical Chem. Russia*, 1948, **22**, 171.

⁵⁰ L. S. Echols and R. N. Pease, *J. Amer. Chem. Soc.*, 1939, **61**, 1024.

⁵¹ S. J. Magram and H. A. Taylor, *J. Chem. Physics*, 1941, **9**, 755.

⁵² H. A. Taylor and H. Bender, *ibid.*, p. 761.

⁵³ E. W. R. Steacie and G. T. Shaw, *ibid.*, 1935, **3**, 344.

⁵⁴ H. A. Taylor and C. Tanford, *ibid.*, 1944, **12**, 47.

⁵⁵ J. S. A. Forsyth, *Trans. Faraday Soc.*, 1941, **37**, 312.

⁵⁶ J. E. Hobbs, *Proc. Roy. Soc.*, 1938, **A**, **167**, 456.

⁵⁷ Cf. N. A. Milas and D. M. Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205, 643; P. George and A. D. Walsh, *Trans. Faraday Soc.*, 1946, **42**, 94.

⁵⁸ R. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 88, 2767; F. F. Rust, F. H. Seubold, and W. E. Vaughan, *ibid.*, p. 95.

energy in the peroxide is calculated to be 39 kcal. so the rate-determining step is taken to be unimolecular fission at the O-O bond. The frequency factor of the Arrhenius equation has the high value of 3.2×10^{16} .^{58a} The pyrolysis of di-*tert.*-amyl peroxide is approximately first order, the activation energy for the initial step being 37—41 kcal. The inclusion of added compounds (*e.g.*, hydrocarbons) with the decomposing peroxides is a valuable means of studying the interactions of free radicals with those compounds. For instance, the vapour-phase addition of hydrogen chloride to ethylene, by a free-radical mechanism, may be induced by di-*tert.*-butyl peroxide.

First order has been assigned to the decompositions of glyoxal tetraacetate,⁵⁹ isopropyl formate,⁶⁰ *tert.*-butyl acetate and propionate,^{60a} isopropyl chlorocarbonate,⁶¹ digermane,⁶² and tetramethyltin (no inhibition of primary process by nitric oxide).⁶³ The dehydrochlorinations of 1:2-dichloroethane, ethyl chloride, and 1:1-dichloroethane^{63a} are of first order. The first of these (retarded by propene and by *n*-hexane) has a free-radical chain mechanism; the two latter appear to be genuine unimolecular decompositions.

Order 1.5 is ascribed to the decompositions of trimethylaluminium⁶⁴ and tetrahydrofuran (nitric oxide does not inhibit, but catalyses when in large amount; so does propylene).⁶⁵

The pyrolysis of hydrocarbons is dealt with, in detail, by Steacie.² More recent work includes the following: (1) the decomposition of *n*-heptane⁶⁶ by a flow method (first order, using kinetic equations of H. M. Hulburt),⁶⁷ giving products in agreement with the theories of F. O. Rice; and of isobutane^{67a} (some retardation by propylene); (2) the decomposition of cyclohexene, cyclohexane, methylcyclopentane, and cyclopentane⁶⁸ (all uninfluenced by nitric oxide; rate-determining steps, first order), and of cyclopentene^{68a} (no inhibition by nitric oxide); (3) the demonstration^{41, 69}

^{58a} For a suggestion about high-frequency factors, see M. Szwarc, *J. Chem. Physics*, 1949, **17**, 107.

⁵⁹ J. C. Arnell, J. R. Dacey, and C. C. Coffin, *Canadian J. Res.*, 1940, **B**, **18**, 410.

⁶⁰ R. B. Anderson and H. H. Rowley, *J. Physical Chem.*, 1943, **47**, 454.

^{60a} E. Warrick and P. Fugassi, *ibid.*, 1948, **52**, 357, 1314.

⁶¹ A. R. Choppin and E. L. Comper, *J. Amer. Chem. Soc.*, 1948, **70**, 3797.

⁶² H. J. Emeléus and H. H. G. Jellinek, *Trans. Faraday Soc.*, 1944, **40**, 93.

⁶³ C. E. Waring and W. S. Horton, *J. Amer. Chem. Soc.*, 1945, **67**, 540.

^{63a} D. H. R. Barton, *J.*, 1949, 148; D. H. R. Barton and K. E. Howlett, *ibid.*, 155, 165.

⁶⁴ L. M. Yeddapanalli and C. C. Schubert, *J. Chem. Physics*, 1946, **14**, 1.

⁶⁵ C. H. Klute and W. D. Walters, *J. Amer. Chem. Soc.*, 1946, **68**, 506.

⁶⁶ W. G. Appleby, W. H. Avery, and W. K. Meerbott, *J. Amer. Chem. Soc.*, 1947, **69**, 2279.

⁶⁷ *Ind. Eng. Chem.*, 1944, **36**, 1012.

^{67a} A. D. Stepukhovich, *J. Gen. Chem. Russia*, 1945, **15**, 341.

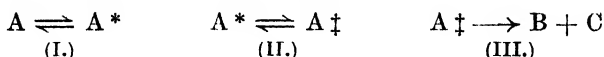
⁶⁸ L. Küchler, *Trans. Faraday Soc.*, 1939, **35**, 874; *Z. physikal. Chem.*, 1943, **B**, **58**, 307; G. R. Schultze and G. Wassermann, *Z. Elektrochem.*, 1941, **47**, 774.

^{68a} D. W. Vanas and W. D. Walters, *J. Amer. Chem. Soc.*, 1948, **70**, 4035.

⁶⁹ C. N. Hinshelwood, Faraday Society Discussion, 1947, **2**, 111; R. G. Partington, *ibid.*, p. 114.

that the rates of the chain-inhibited decompositions of saturated paraffins are almost independent of molecular size and shape for molecules larger than propane (in contrast to oxidation rates); (5) the unimolecular fission of toluene to form a hydrogen atom and a benzyl radical, and corresponding reactions for xylenes and the picolines, yielding information about bond strengths and resonance energies of radicals;⁷⁰ (6) the application of the mass-spectrometer⁷¹ to the study of intermediates formed in the decomposition of hydrocarbons.

Theory of unimolecular processes. A unimolecular reaction may be considered to consist of the following three steps :



Step (I) represents the acquisition of (at least) a critical amount of energy by the molecule (sometimes referred to as "energisation"), (II) the localisation of the critical energy in a particular bond (activation), and (III) the actual dissociation.

Some attempts have been made in the period under review to obtain a better understanding of these individual steps. Either step (II) (case 1) or step (III) (case 2) may be rate-determining; and in step (II) the probability of activation of an "energised" molecule may have a constant value, independent of the excess of energy over the critical amount, or it may be equal to the (statistical) probability that (at least) the critical amount of energy is concentrated in one oscillator, while the remainder of the energy is shared among the other oscillators of the molecule (O. K. Rice and H. C. Ramsperger;⁷² L. S. Kassel⁷³). M. G. Evans and G. S. Rushbrooke⁷⁴ have shown that both for case 1 and for case 2—the validity of the second hypothesis being assumed—the rate constant can be expected to be of the order of $10^{13} \cdot e^{-E_0/kT}$; the distinction between case 1 and case 2 is thus not a useful one. On the other hand, D. D. Eley⁷⁵ has suggested that such a distinction could be made by determining whether the temperature coefficient of the activation energy is positive or negative.

Comparing Kassel's treatment with the transition state method, Evans and Rushbrooke ascribe the discrepancy between the two to the fact that a dissociating bond does not vibrate harmonically (as assumed by Kassel) and that, consequently, the entropy of activation for this model is too low; the two methods are equivalent if allowance is made for this factor.

R. M. Barrer⁷⁶ has investigated the mechanism of step (II) for an idealised model: the molecule is considered to consist of a number of harmonic oscillators of equal frequency, which can exchange energy quanta by "vibrational collisions." Making special assumptions concerning the probability for the transfer of quanta between oscillators, it is possible to

⁷⁰ M. Szwarc, Faraday Society Discussion, 1947, 2, 39; *J. Chem. Physics*, 1948, 16, 128; J. S. Roberts and M. Szwarc, *ibid.*, p. 981.

⁷¹ G. C. Eltenton, *ibid.*, 1947, 15, 455.

⁷² *J. Physical Chem.*, 1928, 32, 225.

⁷³ *Ibid.*, 1943, 39, 168.

⁷⁴ *J. Amer. Chem. Soc.*, 1927, 49, 1617.

⁷⁵ *Trans. Faraday Soc.*, 1945, 41, 621.

⁷⁶ *Ibid.*, 1948, 44, 399.

calculate how much time will elapse before a given initial energy distribution is replaced by one in which a critical number of quanta is accumulated in the "breakable" oscillator. The rather cumbersome calculations lead to the result that the relatively greatest contribution to the reaction rate comes from molecules whose energy considerably exceeds the critical amount.

A more powerful method has been applied to the calculation of the first-order rate constant by N. B. Slater.⁷⁷ If dissociation occurs when the extension of a bond is greater than q_0 , the absolute rate can be calculated by finding the frequency with which the normal vibrations of the molecule will combine in such a way as to make the extension of the bond (q_1) greater than q_0 .

According to the theory of small vibrations

$$q_1 = F(t) = \sum_s \alpha_s \sqrt{\varepsilon_s} \cos 2\pi (\nu_s t + \psi_s)$$

where ν_s is the s th normal frequency and ψ_s the corresponding phase angle. The activation energy E_0 is the smallest value of the sum $\sum_s \varepsilon_s = E$ for which the condition $\sum_s |\alpha_s| \sqrt{\varepsilon_s} = q_0$ can be fulfilled. This turns out to be $E_0 = B/2B_{11} \cdot q_0^2$, where B is the determinant $||b_{rs}||$ and B_{11} the cofactor of b_{11} formed from the coefficients of the expression for the potential energy in terms of "internal" (e.g., stretching and bending) co-ordinates, $V = \frac{1}{2} \sum_{r,s} b_{rs} q_r q_s$.

To obtain the rate constant, it is necessary to calculate the average frequency of attainment of the critical extension for any particular distribution of energy ($\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n$) over the n modes of the molecule and then to average over all possible values of $\varepsilon_1, \varepsilon_2, \dots, \varepsilon_n$ (assuming thermodynamic equilibrium). The result for the rate constant is $k = \nu \cdot e^{-E_0/RT}$; ν is of the order of 10^{13} sec^{-1} and can be expressed explicitly as $\nu = \frac{1}{2\pi} \sqrt{A_{11} B / A B_{11}}$, where B_{11} and B have the same meaning as above, and A_{11} and A are defined in an analogous manner by means of the coefficients a_{rs} of the expression for the kinetic energy $\frac{1}{2} \sum_{r,s} a_{rs} \dot{q}_r \dot{q}_s$. An alternative formula for ν is $(\nu_1 \nu_2 \dots \nu_n) / (\nu_2' \nu_3' \dots \nu_n')$; ν_1, ν_2 are the normal frequencies, $\nu_2', \text{ etc.}$, the normal frequencies of the system when q_1 has the fixed value q_0 .

A particularly simple case arises when the potential energy of the dissociating bond is independent of the potential energy of the rest of the molecule: V becomes $\frac{1}{2}(b_{11}q_1^2 + \sum_s b_{rs}q_r q_s)$, $E_0 = b_{11}q_0^2$ and $\nu = 1/2\pi \cdot \sqrt{b_{11}/m}$ (m is the reduced mass of the two atoms sharing the breaking bond): the molecule behaves like a diatomic one (with respect to decomposition). This result was also obtained some time ago by H. Pelzer,⁷⁸ who used a similar but less general method.

⁷⁷ *Proc. Camb. Phil. Soc.*, 1939, **35**, 56; *Nature*, 1947, **159**, 264; **160**, 576; *Proc. Roy. Soc.*, 1948, **A**, **194**, 112.

⁷⁸ *Z. Electrochem.*, 1933, **39**, 608; *Nature*, 1947, **160**, 576.

Slater's treatment can be translated into the formalism of the transition-state theory by writing $k = v/dq_0 \cdot F^\ddagger'/F$, where F is the partition function of the molecule, F^\ddagger' the partition function of the molecule with the coordinate q_1 between $q_0 - dq_0$ and q_0 , and v the average velocity along q_1 .

Although accurate predictions can perhaps not be expected from a molecular model based on the approximation of classical harmonic oscillators, it is a satisfactory feature of this theory that the frequency factor v is expressed in terms of experimentally accessible parameters (*i.e.*, the coefficients, a_{rs} , b_r , which can be obtained from spectroscopic data).

An interesting empirical correlation between the activation energy of unimolecular decomposition and the vibration frequency of the dissociating bond has been found by P. Fugassi and E. Warrick.⁷⁹ The formula $E_{\text{act.}} = 2.858\bar{5}(35.5 - 900.4\bar{5} \cdot \bar{\nu}/D_e)$ ($\bar{\nu}$ is the observed wave-number of the breaking bond, D_e its dissociation energy obtained by adding the zero-point vibrational energy to the thermochemical bond energy) has been applied in all cases where the necessary data for the weakest bond of the molecule were available; as well as in other cases, where only tentative assignments of observed frequencies could be made. The agreement between calculated and observed activation energies is, on the whole, surprisingly good. The authors do not give a theoretical explanation for the validity of the formula, but they point out that the expression bears a close resemblance to the Morse energy of an anharmonic oscillator:

$$E_{\text{vibr.}} = N\hbar\nu(n + \frac{1}{2}) - (N\hbar\nu)^2(n + \frac{1}{2})^2/4D_e \text{ with } n = 35.$$

The validity of this correlation would seem to lend support to Pelzer's (and Slater's) result that the activation energy depends on the force constant of the breaking bond only—provided its potential energy be not coupled with that of the rest of the molecule. It is, of course, only in this case that an observed frequency can be assigned to the particular bond.

The established theories of chemical kinetics contain the hypothesis that the activated molecules are in thermodynamic equilibrium with the normal molecules (in the absence of chain processes). Some attempts have recently been made to provide a theory not dependent on this assumption. A chemical reaction can be considered as the passage of a representative point in phase space over a potential barrier; the analysis of this problem is analogous to that of a system of Brownian particles escaping by diffusion over an energy barrier (*e.g.*, a repulsive potential) in a viscous medium. H. A. Kramers,⁸⁰ who has developed this argument by classical methods, has shown that for a wide range of conditions, though not for all, the equilibrium hypothesis for the transition state will yield approximately correct results. B. J. Zwolinski and H. Eyring⁸¹ have considered a chemical reaction to be represented by the transitions between a number of quantum states which may be divided into "initial" and "final" states. The kinetic equations applicable to this system are the same as those of a set

⁷⁹ *J. Physical Chem.*, 1942, **46**, 630.

⁸⁰ *Physica*, 1940, **7**, 284.

⁸¹ *J. Amer. Chem. Soc.*, 1947, **69**, 2702.

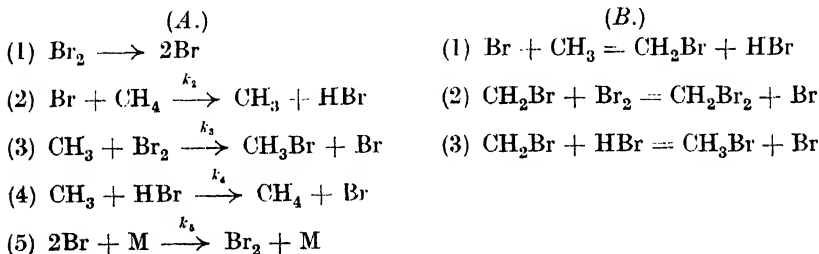
of simultaneous reactions. Calculations made for an idealised model, numerical values being assumed for the transition probabilities, lead to the conclusion that the results of the transition-state theory are not very inaccurate.

J. O. Hirschfelder⁸² considers that the activated state of a unimolecular reaction must be approached by a number of steps involving the acquisition of not more than one energy quantum at a time. The discrepancy between the concentration of activated molecules calculated for this case and the equilibrium concentration of activated molecules is not negligible (the ratio is 0.385), but the difference between the expected reaction rates is not very great.

Although this "non-equilibrium" treatment of chemical reactions would appear to be superior to the "equilibrium" theory from a logical point of view, it cannot yet rival the latter in usefulness.

Chain Reactions.

G. B. Kistiakowsky and E. R. van Artsdalen⁸³ have found that the thermal and photochemical brominations of methane proceed by the same mechanism as the bromination of hydrogen. The initial rate of the thermal reaction at 570° K. is almost the same for both reactions.



The mechanism (A) gives the rate law (first approximation for methyl bromide as sole bromination product) :

$$\frac{d[\text{CH}_3\text{Br}]}{dt} = k \cdot \frac{[\text{CH}_4][\text{Br}_2]^{\frac{1}{2}}}{1 + k_4[\text{HBr}]/k_3[\text{Br}_2]}, \quad (k = K^{\frac{1}{2}}k_2)$$

[K = equilibrium constant for (1)] which is in agreement with observation. Oxygen inhibits the reaction. The activation energy for the photochemical reaction (determined from the rates at 423°, 453°, and 483° K.) is 17.8 kcal.; this is ascribed to reaction (2). The coefficient k_4/k_3 is not independent of temperature as in the hydrogen-bromine reaction. From the temperature coefficient of the hydrogen bromide inhibition, $E_4 - E_3 \sim 2$ kcal. (E_4 , E_3 are the activation energies for k_4 and k_3 , respectively).

The bromination of methyl bromide⁸³ is 7.5–10 times faster than that of methane; it is not inhibited by hydrogen bromide. The observed activation energy of 15.6 kcal. is attributed to step (1) of the scheme (B).

⁸² *J. Chem. Physics*, 1948, 16, 22.

⁸³ *Ibid.*, 1944, 12, 469.

Calculations carried out by means of a reasonable model for the transition state of (1) give a rate which is in excellent agreement with the observed one.

Although only the photochemical bromination of ethane has been investigated,⁸⁴ it is probable—by analogy with methane—that, in this case too, the thermal reaction would follow the same mechanism. Here, however, the constants of the Bodenstein–Lind expression show trends.

The data obtained from the kinetic analysis of the bromination of methane⁸³ and ethane⁸⁴ have been used to calculate the bond strengths of the C–H bonds as 102 and 98 kcals., respectively.

Another reaction following this type of rate law is $\text{H}_2 + (\text{CN})_2 = 2\text{HCN}$ ⁸⁵ at 550–675°. There is no trouble due to polymerisation of $(\text{CN})_2$, but the reaction is at least partly heterogeneous below 650°. Apart from an induction period and failure at low pressures, the equation

$$\frac{1}{2} \cdot \frac{d[\text{HCN}]}{dt} = \frac{k[\text{H}_2][(\text{CN})_2]^{\frac{1}{2}}}{1 + 0.25[\text{HCN}]/2[(\text{CN})_2]}$$

is obeyed approximately, while the constants for 1.5 order fall sharply with time when the ratio $[\text{H}_2]/[(\text{CN})_2]$ is high. The activation energy is 73 kcals. The mechanism is exactly the same as for the hydrogen–bromine reaction, if Br_2 is replaced by $(\text{CN})_2$.

The nitrogen–oxygen reaction. The oxidation of nitrogen introduced into explosive mixtures has been investigated by J. Zeldovich.⁸⁶ The results reported and the ingenious kinetic analysis relate to the interaction of nitrogen and oxygen in a system whose temperature is falling.

From the yields of nitric oxide in the reaction products of different explosive mixtures of nitrogen, oxygen and some gaseous “fuel” the following facts are established: (1) The yield of nitric oxide is strongly correlated with the concentration of nitrogen and the concentration of oxygen remaining after the combustion of the fuel. (2) The nature of the fuel used (*e.g.*, H_2 , CO, CH_4 , etc.) does not influence the amount of nitric oxide produced, except in so far as the reaction temperature is affected. (3) In independent flow experiments analysis of samples taken at different points in a rapid stream of burning gas shows that the exothermal combustion is virtually completed in 10^{-3} sec., before measurable amounts of nitric oxide are formed (the oxidation of nitrogen ceases after 10^{-2} sec.). (4) The yield of nitric oxide is always smaller than the equilibrium concentration at the (calculated) highest temperature attained during the explosion.

The nitrogen–oxygen reaction is reversible; and the rate of decomposition of nitric oxide was determined by measuring the yield of NO in mixtures to which nitrogen dioxide had been added initially. Extrapolation of the data on the rate of decomposition of nitrogen dioxide⁸⁷ into nitric oxide

⁸⁴ H. C. Andersen and E. R. Van Artsdalen, *J. Chem. Physics*, 1948, **16**, 479.

⁸⁵ N. C. Robertson and R. N. Pease, *J. Amer. Chem. Soc.*, 1942, **64**, 1880.

⁸⁶ *Acta Physicochim. U.R.S.S.*, 1946, **21**, 577; cf. M. V. Polyakov, L. A. Kostyuchenko, and D. S. Nosenko, *J. Physical Chem. Russia*, 1944, **18**, 115.

⁸⁷ M. Bodenstein and H. Ramstetter, *Z. physikal. Chem.*, 1922, **100**, 106.

and oxygen shows that decomposition will be complete in less than 10^{-8} sec. in the relevant temperature range; consequently, the final concentration of nitric oxide is greater or less than its initial concentration depending on the amount of nitrogen dioxide added initially. The "critical" concentration of nitric oxide, defined as that which is not changed by the reaction, depends on the maximum temperature (T_m) reached; if this is below 2500°K. the "critical" concentration is comparable to the equilibrium concentration at T_m ; it is relatively much smaller at higher temperatures.

The approximate activation energy for the decomposition of nitric oxide is obtained as follows: if the reaction is reversible and bimolecular

$$d[\text{NO}]/dt = k'[\text{N}_2][\text{O}_2] - k[\text{NO}]^2 \quad . \quad . \quad . \quad (1)$$

At the "critical" concentration of nitric oxide (denoted by $\{ \}$), $k'[\text{N}_2][\text{O}_2] = k[\text{NO}]^2$, since $d[\text{NO}]/dt = 0$ (approximately). Making the simplifying assumption that the reaction proceeds for τ seconds at T_m and then stops, (1) can be integrated: this gives $k\tau$ as a function of the "critical" concentration and of the final concentration of nitric oxide. If $k\tau$ is plotted against $1/T_m$ a fairly straight line is obtained (2000 — 2900°K.). The activation energy (A) determined in this manner is 82 ± 10 kcal./mole. The activation energy for the formation of nitric oxide (A') equals $A + 2E$, where E is the known heat of the reaction: $A' = 82 \pm 10 + 2 \times 21.4 = 125 \pm 10$ kcal.

The remainder of the analysis is carried out with the aid of these results and some ingenious dimensional considerations.

Let $[\text{NO}]_i$ denote the equilibrium concentration and k the rate constant for decomposition at the instantaneous temperature, and $[\text{NO}]_e$ the equilibrium concentration and k_m the rate constant at T_m . The rate equation can be written

$$d[\text{NO}]/dt = k[\text{NO}]_i^2 - k[\text{NO}]^2 \quad . \quad . \quad . \quad (2)$$

It is supposed that k/k_m and $[\text{NO}]_i/[\text{NO}]_e$ depend on the dimensionless time variable t/τ only (τ is as yet unspecified); $k/k_m = f_1(t/\tau)$; and $[\text{NO}]_i/[\text{NO}]_e = f_2(t/\tau)$ for all reaction mixtures. Thus (2) becomes

$$\frac{d([\text{NO}]/[\text{NO}]_e)}{d(t/\tau)} = k_m[\text{NO}]_e^2 f_1\left(\frac{t}{\tau}\right) \left[f_2^2\left(\frac{t}{\tau}\right) - \frac{[\text{NO}]^2}{[\text{NO}]_e^2} \right] \quad . \quad . \quad (3)$$

It can be shown that (3) would hold for all reactions of this type (carried out in the same system) provided the cooling law

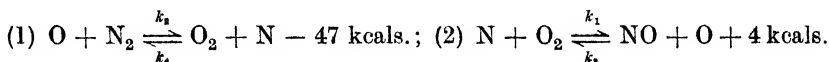
$$dT/dt = -aT^2 \text{ or } 1/T = 1/T_m + at \quad . \quad . \quad . \quad (4)$$

is valid. This cooling law has in fact been verified by independent experiments. Substituting $De^{-A/RT}$ for the rate constant k and $Be^{-E/RT}$ for the equilibrium constant $K = [\text{NO}]_i/([\text{N}_2][\text{O}_2])^{1/2}$, one can eliminate f_1 and f_2 from (3), using (4):

$$\frac{d([\text{NO}]/[\text{NO}]_e)}{d(t/\tau)} = k_m[\text{NO}]_e^2 e^{-4t/\theta\tau} \left\{ e^{-2t/\theta\tau} - \frac{[\text{NO}]^2}{[\text{NO}]_e^2} \right\} \quad . \quad . \quad (5)$$

where τ can now be identified with $R/(A + 2E)a \sim R/6Ea$ (since $A \sim 4E$). Equation (5) can be integrated by means of approximate methods. The curve thus obtained for the variation of $[\text{NO}]/[\text{NO}]_e$ with T_m is very similar to the observed one; the deviation of 12–13% for large yields is attributed to the inhomogeneity of the temperature distribution.

Calculation of the cross-sectional area for the bimolecular reaction of nitrogen and oxygen, however, gives a value about 1000 times too large (i.e., 3×10^{-13} cm.²). The following chain mechanism has therefore been suggested to the author by Semenov:



k_1/k_3 and k_2/k_4 may be calculated by statistical mechanics. Introducing the calculated values for these, assuming equilibrium with respect to the dissociation of oxygen, and neglecting a term $k_3[\text{NO}]$ in a sum $k_3[\text{NO}] + k_2[\text{O}_2]$ (since $[\text{NO}] \ll [\text{O}_2]$), the stationary state method gives:

$$d[\text{NO}]/dt = 5 \times 10^{11} [\text{O}_2]^{-\frac{1}{2}} \cdot e^{-86,000/RT} \{[\text{O}_2][\text{N}_2] \cdot 21 \cdot e^{-43,000/RT} - [\text{NO}]^2\} \\ 1. \cdot 10^{-1} \text{ mol. sec.}^{-1} \quad (6)$$

This rate law differs from the bimolecular equation first assumed only by the factor $[\text{O}_2]^{-\frac{1}{2}}$. Experiments designed to investigate the effect of the oxygen pressure over a wide range gave results in fair agreement with (6). The chain mechanism is compatible with reasonable cross-sectional areas for the collisions.

Branching-chain Reactions.

The Hydrogen-Oxygen Reaction.—The general features of the thermal reaction between hydrogen and oxygen are well known.⁸⁸ At temperatures between 500° and 600° C., a very slow reaction at low pressures gives place to an explosion at the "first explosion limit" (pressure of a few mm.). At the "second explosion limit" (about 100 mm. in a silica vessel at 550°), explosion gives way to a reaction of measurable speed. The numerical values of both limits vary with temperature; and, on a pressure-temperature graph, the curves for the first and the second limit meet, forming a continuous curve, bounded on the low-temperature side, which encloses a region—referred to by some writers as the "explosion peninsula"—in which explosion occurs. It is well established that the first limit occurs where the concentrations of radicals formed in branching chains are no longer kept stationary by surface deactivation, and that the second limit occurs where a reaction in the gas phase prevents further effective branch-

⁸⁸ C. N. Hinshelwood and A. T. Williamson, "The Reaction between Hydrogen and Oxygen," Oxford, 1934; N. Semenov, "Chemical Kinetics and Chain Reactions," Oxford, 1935; B. Lewis and G. von Elbe, "Combustion, Flames and Explosions of Gases," Cambridge, 1938; W. Jost, "Explosion und Verbrennungsvorgänge in Gasen," Berlin, 1939; L. S. Kassel, *Chem. Reviews*, 1937, **21**, 331.

ing of the chains. Above the second limit, the reaction is again controlled by deactivation of chain carriers at the vessel wall. At still higher pressures, explosion again occurs. This can be due to breakdown of isothermal conditions; but, even if isothermal conditions are maintained, a "third explosion limit" is to be expected, on theoretical grounds, at which branching of chains gets out of control. Evidence for a third limit has now been obtained; and it appears that it is controlled by the extent to which chain carriers are deactivated at the surface.

Coated reaction vessels. Recent work has made use of the observation by R. N. Pease⁸⁹ (in flow experiments) that the thermal combination of hydrogen and oxygen is greatly retarded (up to 2000-fold) if the reaction vessel is rinsed, before use, with potassium chloride solution. In Pease's experiments the rinsing also eliminated the formation of hydrogen peroxide, which otherwise appeared at 530—550° in the region of slow reaction. A. A. Frost and H. N. Alyea,⁹⁰ working with a Pyrex-glass vessel previously rinsed with a 10% potassium chloride solution, observed an increase in the first explosion limit of about 5-fold compared with earlier values in silica vessels. In more recent work, visible, coherent salt deposits have been used; and their effect upon the first limit has been confirmed by A. H. Willbourn and C. N. Hinshelwood.¹⁰⁰ Using various salts at 500°, these authors have found increases in the first limit up to 18-fold, as compared with an uncoated silica vessel. They find relative efficiencies to be $\text{Cs}^+ > \text{K}^+ > \text{Ba}^{++}, \text{Ca}^{++}$ and $\text{I}^- > \text{F}^-, \text{Br}^-, \text{SO}_4^{--}, \text{Cl}^-$, the effect of iodide being particularly marked. Clearly, the effects are due to much enhanced efficiency of chain-breaking at the salt surfaces. Correspondingly, Willbourn and Hinshelwood find the effect of the salts KCl, KI, CsCl, and CsI upon the second explosion limit to be very small, there being a slight depression, the more noticeable the higher the temperature. However, G. von Elbe and B. Lewis⁹⁹ find that the explosion region is diminished at both its boundaries by salt coatings, the second limit being appreciably lowered at 500—530° by coating quartz or Pyrex vessels with the salts KCl, BaCl_2 , Na_2WO_4 , and $\text{K}_2\text{B}_2\text{O}_4$. The same workers found that the salts KCl, BaCl_2 , Na_2WO_4 , and $\text{K}_2\text{B}_4\text{O}_7$ reduced the rates of combination of hydrogen and oxygen, at pressures above the second limit, to identical values; $\text{K}_2\text{B}_2\text{O}_4$ was less effective, except under conditions of rapid reaction; but $\text{K}_2\text{B}_2\text{O}_4 + \text{KOH}$ behaved like the other salts. A boric acid surface behaved like clean silica or Pyrex. Von Elbe and Lewis drew the theoretically important conclusion that limiting conditions had been reached where the chain-breaking efficiency of the surfaces had reached a constant maximum efficiency, so that the rate of chain destruction was governed by the rate of diffusion of chain-carriers to the wall. Willbourn and Hinshelwood made a similar assumption in interpreting their own experiments in potassium chloride-coated vessels; but they have pointed out that their assumption cannot be made without reserve, because caesium chloride (rate at 550° = 0.28 mm./min.) retards

⁸⁹ *J. Amer. Chem. Soc.*, 1930, **52**, 5106.

⁹⁰ A. A. Frost and H. N. Alyea, *ibid.*, 1933, **55**, 3227.

the reaction more efficiently than potassium chloride (rate = 0.60). Cullis and Hinshelwood¹⁰⁰ find that iodide-coating completely alters the character of the reaction, probably because of the liberation of minute amounts of iodine, which is known to be an inhibitor of the hydrogen-oxygen reaction (cf. A. B. Nalbandyan¹⁰⁷). The efficient retarding salts have cations which can form hydrides;¹⁰⁰ and hydrogen atoms may be removed by reactions of the type $KX + H = K + HX$, $KX + H = KH + X$. The HO_2 radical might form $H_2O_2 + H$, the H being taken up as hydride and the peroxide being decomposed on the salt surface (cf. Pease⁸⁹). On the other hand, von Elbe and Lewis⁹⁹ have suggested that the chain-breaking efficiency of salt surfaces is due to strong adsorptive forces exerted by them.

The rupture of chains at surfaces has been treated mathematically by N. N. Semenov⁹² and experimentally by A. B. Nalbandyan, in silver (explosions observed, contrary to earlier work) and iron vessels⁹³ and on wires of various materials,⁹⁴ and by W. V. Smith.⁹⁵ Surfaces of ZnO , Cr_2O_3 and graphite are particularly effective in raising the first limit. In a vessel coated with potassium tetraborate, containing a graphite rod, the energy of activation for $H + O_2 = OH + O$ is estimated to be 17.8 kcal.⁹⁴

The practical importance of salt-coated vessels is that they make the reactions both slower and much more reproducible. The theoretically anticipated effects of vessel diameter and gas pressures upon the first and the second explosion limits have been clearly observed in such vessels.

(In connection with surface effects, it is noteworthy that S. von Bogdandy and M. Polanyi⁹⁶ found an *increased* chain length in the hydrogen-chlorine reaction, induced by sodium atoms, when the vessel surface was covered with sodium chloride.)

Mechanism of the hydrogen-oxygen reaction. New investigations with salt-coated vessels⁹⁷⁻¹⁰⁰ have led to firm conclusions about the mechanism of reaction, with a substantial measure of agreement. The present position of the reaction has been reviewed by C. N. Hinshelwood;¹⁰¹ and the estab-

⁹² *Acta Physicochim. U.R.S.S.*, 1943, **18**, 93.

⁹³ *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **32**, 196; 1944, **44**, 328.

⁹⁴ *Ibid.*, 1945, **47**, 202; A. B. Nalbandyan and S. Shubina, *J. Physical Chem. Russia*, 1946, **20**, 1249; cf. V. V. Voevodsky, *ibid.*, p. 779.

⁹⁵ *J. Chem. Physics*, 1943, **11**, 110.

⁹⁶ *Z. Electrochem.*, 1927, **33**, 554.

⁹⁷ M. Prettre, *J. Chim. physique*, 1936, **33**, 189.

⁹⁸ O. Oldenberg and H. S. Sommers, *J. Chem. Physics*, 1939, **7**, 279; 1940, **8**, 468; 1941, **9**, 114, 573; 1942, **10**, 193; cf. F. S. Dainton, *ibid.*, 1941, **9**, 826; *Trans. Faraday Soc.*, 1942, **38**, 227.

⁹⁹ G. von Elbe and B. Lewis, *J. Chem. Physics*, 1939, **7**, 710; H. R. Heiple and B. Lewis, *ibid.*, 1941, **9**, 584; von Elbe and Lewis, *ibid.*, 1942, **10**, 366.

¹⁰⁰ A. H. Willbourn and C. N. Hinshelwood, *Proc. Roy. Soc.*, 1946, **A**, **185**, 353, 369, 376; C. F. Cullis and C. N. Hinshelwood, *ibid.*, **186**, 462, 469.

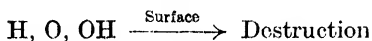
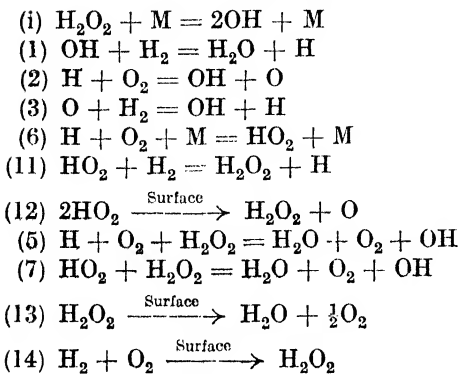
¹⁰¹ C. N. Hinshelwood, *ibid.*, **188**, 1.

lishment of a plausible mechanism has, in turn, given rise to new discussions of the explosive reaction.¹⁰⁵ The mechanisms proposed are :

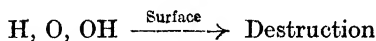
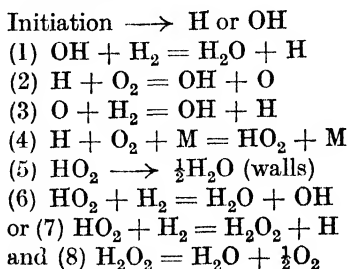
Scheme I

(von Elbe and Lewis).

(Authors' numbering of reactions.)

*Scheme II*

(Willbourn and Hinshelwood).



Agreement is reached on the following points : (a) The principal potential chain-propagating processes are the reactions numbered (1), (2), and (3) in both schemes. They would give rise to branching chains. (b) At pressures up to the first limit, branching is controlled by surface deactivation of H, O, and OH. (c) Control of branching is re-established at the second limit by the reaction labelled (I, 6) and (II, 4). Gaseous recombinations such as $2\text{H} + \text{M} = \text{H}_2 + \text{M}$ are inadmissible.⁹⁹ (d) The radical HO_2 is destroyed at the wall [reactions (I, 12) or (II, 5)], but it may also react with H_2 by reactions (I, 11) and (II, 6) [or II (7)], and one of these processes becomes the principal chain carrier in the reaction at measurable speed above the second explosion limit. Competition between (II, 6) or (I, 11) and surface deactivation of HO_2 accounts for the influence of surface upon the reaction above the second limit. Von Elbe and Lewis argue that, with uncoated surfaces of low chain-breaking efficiency, the lifetime of HO_2 should become large and reaction (I, 11) should become noticeable at pressures around the second limit. Consequently, the value of the second limit should be higher in uncoated than in salt-coated vessels, as, indeed, these authors find experimentally (compare previous section).

The second explosion limit. In scheme (I), the condition for explosion at the second limit reduces to

$$k_6[\text{M}] = 2k_2$$

in which $[\text{M}] = [\text{H}_2] + [\text{O}_2] + [\text{X}]$, X being an inert molecule. At the second limit : ¹⁰²

$$[\text{H}_2] + k_{\text{O}_2}[\text{O}_2] + k_{\text{X}}[\text{X}] = K \quad . \quad . \quad . \quad . \quad (1)$$

In this equation $k_{O_2} = Z_{O_2}/Z_{H_2}$; $k_X = Z_X/Z_{H_2}$, and Z_{H_2} , Z_{O_2} , Z_X are constants proportional, with the simpler gases, to the collision numbers of the respective molecules with the "reaction complex," $H-O_2$; k_{O_2} and $k_X(k_{H_2} = 1)$ can be calculated from the kinetic theory of gases.^{99, 102} They have also been determined experimentally, from measurements of the second explosion limit pressure, by von Elbe and Lewis (I), in potassium chloride-coated Pyrex vessels, for different proportions of hydrogen and oxygen in the reaction mixture, with and without addition of inert gases, at temperatures of 480—570°; and also by Willbourn and Hinshelwood (II) at 550—580°, for uncoated silica and for potassium chloride-coated vessels. The results of the two investigations are compared in the following table:

| Gas, X. | k_X , calc., = Z_X/Z_{H_2} | | k_X , obs. | |
|------------------------|--------------------------------|------|--------------|-------------|
| | I. | II. | I. | II. |
| He | 1.60 | — | 1.80 | — |
| O ₂ | 0.42 | 0.4 | 0.35 | 0.4* —0.325 |
| N ₂ | 0.46 | 0.45 | 0.43 | 0.39*—0.35 |
| CO ₂ | 0.43 | 0.51 | 1.47 | 0.90 |
| H ₂ O | 0.6—0.9 | 0.62 | 14.3 | 11.0* —8.1 |

* Uncoated silica vessel at 550°.

The agreement in the quantitative interpretation of the second explosion limit appears to be excellent, and it supports the postulated mechanism. Nevertheless, this mechanism is not a unique solution, though much the most plausible one.⁹⁹

The two sets of experiments concur in furnishing a value for k_{CO_2} higher than the theoretical one, and also a particularly high value for k_{H_2O} (cf. Nalbandyan,¹⁰⁷ who finds $k_{H_2O} = 5.5$ at 450°). The latter is important, because steam is the reaction product. Even a small amount of water vapour markedly lowers the second limit pressure;⁹¹ and von Elbe and Lewis consider that this fact explains a number of earlier observations upon the hydrogen-oxygen reaction.

The third explosion limit. The formation of OH or H in the processes [(I, 6) and (I, 11); (II, 4) and (II, 6) or (II, 7)] which continue the (stationary) chain reaction, at pressures above the second limit, implies that, at high enough pressures, increased concentrations of H and OH may again cause a branching-chain explosion at a third limit. In uncoated reaction vessels with surfaces of low chain-breaking efficiency, the branching-chain explosion at the third limit is masked by thermal explosions; but, with the slower reactions in potassium chloride-coated vessels, the third limit has been detected and characterised. It occurs at pressures between 400 and 1600 mm. at temperatures between 550° and 610°. Since the principal chain-breaking process, above the second limit, is the surface deactivation of HO₂ [(I, 12); (II, 5)], it may be predicted that explosion at the third limit should be favoured and the third limit pressure should be lowered, by increasing diameter of the reaction vessel. This effect has been verified.^{98, 99} Quantitatively, the influences of the proportions of hydrogen

¹⁰² G. H. Grant and C. N. Hinshelwood, *Proc. Roy. Soc.*, 1933, **A**, **141**, 29.

and oxygen in the reaction mixture, and of added inert gases, upon the value of the third limit pressure, resolve themselves into the influence of gas composition upon the rate of formation of the HO_2 radical in the gas phase (as they do at the second explosion limit), together with the influence of gas composition upon the rate of diffusion of HO_2 to the wall, and with the effect of hydrogen proportion in reaction (II, 6). For the influence of gas composition upon the rate of (II, 4), the constants derived to account for the effects of changing gas composition at the *second limit* can also be used at the *third limit*. This procedure has been employed both by von Elbe and Lewis and by Willbourn and Hinshelwood. It involves the assumption, made in both investigations, that the chain-breaking efficiency of the salt surface is so high that the rate of diffusion determines the rate of destruction of the chain carrier. The validity of this assumption has already been commented on.

Taking the reaction mechanism to be composed of the steps (II, 1)—(II, 6), the rate of formation of steam is given by equation (3), below.¹⁰⁰ The condition for explosion is that the denominator in the expression on the right-hand side of this equation should be zero; *i.e.*,

$$2k_2/\Sigma k_4[M] = k_5/(k_6[\text{H}_2] + k_5)$$

in which

$$\Sigma k_4[M] = k_4'([\text{H}_2] + k_{\text{O}_2}[\text{O}_2] + k_{\text{X}}[\text{X}]).$$

Using relative diffusion coefficients $D_{\text{X}}' = D_{\text{H}_2}/D_{\text{X}}$, which can be derived from the kinetic theory of gases, the condition for explosion, at a given temperature, reduces to

$$\frac{[\text{H}_2] + D_{\text{O}_2}'[\text{O}_2] + D_{\text{X}}'[\text{X}]}{1 + k_{\text{O}_2}\rho_{\text{O}_2} + k_{\text{X}}\rho_{\text{X}} - K/[\text{H}_2]} = C \quad . \quad . \quad . \quad (2)$$

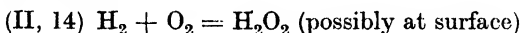
in which $\rho_{\text{X}} = [\text{X}]/[\text{H}_2]$, K is identical with the constant K in equation (1), and C is a constant which must be found from experiments on the third limit itself. Willbourn and Hinshelwood have applied equation (2) to their results for the effects of hydrogen-oxygen proportion and of admixed nitrogen, carbon dioxide, and water vapour upon the value of the third limit pressure at 586°. They find that the constants which must be inserted in equation (2) to give the best fit between the theoretical and the experimental curves are not far removed from the theoretical constants and those determined from measurements at the second limit. It is noteworthy that the experimental curve for the influence of 100 mm. of carbon dioxide upon the third limit at varying proportions of hydrogen to oxygen is quite different in form from the corresponding curve for 100 mm. of nitrogen (nitrogen lowers the third limit pressure); and that the general theoretical equation (2) reproduces this difference in form when suitable constants are inserted. The form is governed by the value of k_{X} .

More elaborate equations—corresponding to the more elaborate scheme (I)—have been successfully applied to the third limit by von Elbe and Lewis. For these, reference must be made to the original paper. These

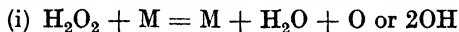
authors point out that values of the third limit pressure may be distorted by two contradictory factors, namely, a thermal influence in the very rapid reactions (just below the explosion limit, rates as high as 80—100 mm. of water per min. were observed), tending to displace the third limit to lower pressures; and the formation of steam, which should raise the third limit for the same reason that it depresses the second limit (high k_{H_2O}). However, in the experiments of Willbourn and Hinshelwood water vapour lowered the third limit pressure. This result, accompanied by a reduction of the constant C of equation (2), was ascribed to an effect of water upon the potassium chloride-coated surface, reducing its chain-breaking efficiency.

Von Elbe and Lewis state that the third limit pressure is independent of the nature of the surface, if it is heavily coated with any of the salts used by them. They find that the third limit explosion is preceded by an induction period, during which a rapid reaction occurs. The induction period (up to 70 seconds) is small near the junction of the second and the third limits and increases towards lower temperatures.

The chain-initiation process. Nothing has so far been said about how the chains are started. Von Elbe and Lewis reject the dissociation of hydrogen into atoms as chain initiator, on the ground that the temperature coefficient of the reaction, in a range uninfluenced by explosion limits, gives an overall activation energy of the order of only 100 kcal., which they hold to be insufficient to include the activation energies both of chain continuation and of chain initiation, if the latter is the dissociation of hydrogen molecules. Instead, they suggest that a spontaneous reaction (heterogeneous or gaseous) in the first brief stage preceding the establishment of stationary concentrations supplies atoms which react by the processes (I, 6), (I, 12), and (I, 11) to form hydrogen peroxide. They summarise this stage by the equation



and they consider that the steady-state initiation reaction is



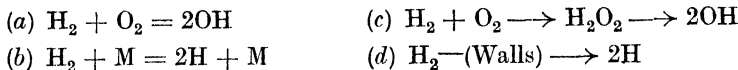
Willbourn and Hinshelwood¹⁰⁰ treat the initiation reaction in a novel manner. Their reaction scheme (II) leads to the equation

$$\frac{d[H_2O]}{dt} = \frac{f_1 \left\{ \frac{1.5k_5 + 2k_6[H_2]}{k_5 + k_6[H_2]} \right\}}{1 - \frac{2k_2}{\Sigma k_4[M]} - \frac{k_6[H_2]}{k_5 + k_6[H_2]}} \quad \cdot \quad \cdot \quad \cdot \quad (3)$$

in which f_1 is the rate of the initiation reaction. A function R^* is defined such that $d[H_2O]/dt = 2f_1R^*$. With the expressions for $\Sigma k_4[M]$ and for k_5 used in treating the experiments at the third explosion limit, R^* is given by an expression involving the gas composition and the constants k_x , D_x' , K , and C of equations (1) and (2), already evaluated at the third limit. The function R^* can thus be calculated, without reference to experiments on the

rate of reaction. The rate of reaction is proportional to $(f_1 R^*)$, so the variation of reaction rate with the pressures of hydrogen, oxygen, and inert gases can be *calculated* for different possible forms of the function f_1 . Comparison with the *observed* influence of these variables upon the rate should indicate the correct form of f_1 .

At the temperature of the experiments ($>560^\circ$) chain initiation in the gas phase is thought to be possible. Four processes are considered :



Of these, reaction (b), as chain initiator, gives much the best agreement between experiment and calculation. For this case, the function f_1 takes the form

$$f_1 = k[\text{H}_2](Z_{\text{H}_2}[\text{H}_2] + Z_{\text{O}_2}[\text{O}_2] + Z_{\text{X}}[\text{X}])$$

where Z_{H_2} , Z_{O_2} , and Z_{X} are the relative collision numbers for hydrogen molecules, respectively, with hydrogen, oxygen, and an inert gas X. The Z values are calculated from kinetic theory.

Cullis and Hinshelwood¹⁰⁰ have measured rates of reaction at different temperatures (560 — 596°) and have calculated R^* at each temperature from third-limit data. They have thus obtained the temperature coefficient of f_1 and are able to calculate, directly, the activation energy for the initiation reaction. They find this to be 100 kcal. for potassium chloride-coated vessels and 92 kcal. for caesium chloride-coated vessels. They regard the former value as the more reliable and consider that the result supports the view that the dissociation of hydrogen into atoms is the initiation step under the conditions of their experiments. (Third-limit pressures are higher for caesium than for potassium chloride.) P. G. Ashmore and F. S. Dainton^{102a} support this conclusion. They find 134 and 123 kcal. for the activation energy of initiation at two different gas pressures.

The measurable reaction between the second and the third explosion limits. The schemes (I) and (II) concur in attributing the major part in the continuing reaction above the second limit to the steps (I, 6), (I, 11), and (I, 12) or (II, 4) with (II, 5) and (II, 6) or (II, 7). To preserve a steady concentration of hydrogen peroxide, von Elbe and Lewis introduce the steps (I, 7) and (I, 5), together with (I, 13) (because hydrogen peroxide is known to decompose heterogeneously).¹⁰³ They have formulated equations for the reaction velocity to correspond with scheme (I) and have tested them experimentally with generally satisfactory results.

In uncoated silica or Pyrex vessels, the reaction above the second limit shows auto-acceleration in its early stages, and is often not easily reproducible in speed. In salt-coated vessels, the reactions are, as a rule, not auto-accelerated, but proceed at a constant rate for an appreciable time. The rates are reproducible.

^{102a} *Nature*, 1946, **158**, 416.

¹⁰³ Cf. R. C. Mackenzie and M. Ritchie, *Proc. Roy. Soc.*, 1946, **A**, **185**, 207.

To account for the auto-acceleration, V. V. Voevodsky¹⁰⁴ adds the reaction $\text{HO}_2 + \text{H}_2\text{O} = \text{H}_2\text{O}_2 + \text{OH}$ to the scheme (I), with the supposition that it is an easier reaction than (I, 11). In uncoated vessels, the difficulty of step (I, 11) leads to an accumulation of HO_2 radicals (calculated to attain a partial pressure of nearly 3 mm. near the beginning of the reaction) and combination is slow. The small amounts of water formed enter easily into reaction with HO_2 , forming OH. The reaction accelerates and the concentration of HO_2 falls.

The explosive reaction between the first and the second limits. The reaction in this region has been discussed by N. N. Semenov.¹⁰⁵ Explosion is preceded by a period of auto-acceleration, during which, according to Semenov, $\Delta p = Ce^{\phi t}$. The experiments of A. Kovalsky,¹⁰⁶ at pressures near the first limit, confirmed this and gave values for ϕ at different temperatures and initial pressures. Adopting, for the reaction mechanism, the steps $\text{H}_2 + \text{O}_2 = 2\text{OH}$, followed by (I, 1, 2, 3, 6), with wall deactivation of H and HO_2 , Semenov¹⁰⁵ derives equations for the reaction rate, at pressures not greatly exceeding the first limit pressure. On introducing experimental results for ϕ , p_1 , and p_2 (the first and the second limit pressures), the equations lead to quantitative deductions, which are in approximate agreement with experiment. Approximate agreement is also obtained at higher pressures (still between the first and second limits), though experiments are very difficult here, because of thermal effects. Experiments of A. B. Nalbandyan¹⁰⁷ (made with a sensitive membrane manometer, furnishing photographic records) give induction periods of <0.1 to 0.4 sec. (decreasing towards the middle of the explosion region and increasing near the explosion limits), whose values are in accord with theoretical calculation. Neither the nature of the wall (in potassium chloride-coated and stainless-steel vessels), nor the presence of water vapour, influences the temperature dependence of the induction period inside the explosion peninsula, and of ϕ . Water therefore does not react chemically with the active centres.

Semenov's equations^{107a} also furnish rates for individual steps in the mechanism (see below), and an estimate of the concentration of hydrogen atoms present at various stages of the explosive reaction. The remarkable conclusion is reached that for stoichiometric mixtures at initial pressure $p_0 = 1.43p_1$, $2p_1$, and $4p_1$, 5, 15, and 40%, respectively, of the initial hydrogen is present as hydrogen atoms (cf. von Elbe and Lewis's⁹⁹ estimates for the partial pressure of hydrogen atoms during the slow reaction; e.g., at 560° , $p_{\text{H}} = 9.7 \times 10^{-4}$ mm. at total pressure 170 mm.).

Experimental support is put forward for the prevalence of high con-

¹⁰⁴ J. *Physical Chem. Russia*, 1946, **20**, 1285.

¹⁰⁵ N. N. Semenov, *Bull. Acad. Sci. U.R.S.S., Cl. Sci. Chim.*, 1945, 210; *Compt. rend. Acad. Sci. U.R.S.S.*, 1944, **43**, 342; **44**, 62, 241.

¹⁰⁶ *Physikal. Z. Sovietunion*, 1932, **1**, 595; 1933, **4**, 723.

¹⁰⁷ *Acta Physicochim. U.R.S.S.*, 1944, **19**, 483, 497; 1945, **20**, 31; cf. Kondratyev, *Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **49**, 116.

^{107a} *Acta Physicochim. U.R.S.S.*, 1945, **20**, 291.

centrations of hydrogen atoms in mixtures reacting within the explosion peninsula. In the first place, this rests on the estimation of OH-radical concentration by absorption spectroscopy.¹⁰⁸ Estimates by L. I. Avramenko and V. N. Kondratév¹⁰⁹ were shown by O. Oldenberg and F. F. Rieke¹¹⁰ to need re-interpretation. Taking this into account, later work by Avramenko¹¹¹ leads to the conclusion that in a hydrogen-oxygen flame, at total pressure about 40 mm. (flame temperatures 900—1370° K.), the OH-radical concentration exceeds 10⁴ times the thermodynamic equilibrium value and is thus brought into being by the chemical reaction. On the supposition that the partial pressure of OH radicals (p_{OH}) may amount to 0.1% of the initial oxygen pressure,^{105, 112} it is deduced from the relative rates of the reactions (b) and (c), below, that p_{H} should be 40—200 times p_{OH} , which means that p_{H} is 4—20% of the initial hydrogen pressure, in approximate agreement with the above theoretical estimate. (In mixtures undergoing *slow* reaction at about 1 atm. pressure and 550°, O. Oldenberg, E. G. Schneider, and H. S. Sommers¹¹³ detected no OH radicals by absorption spectroscopy and concluded that their concentration was less than one radical in 300,000 molecules.)

Kondratév¹¹⁴ furnishes experimental evidence of a different kind. A thermocouple inside a thin quartz tube, coated with ZnO, Cr₂O₃, is exposed to the reaction mixture. The heat of recombination of hydrogen atoms upon this particularly efficient catalytic surface^{94, 95} is registered as a temperature difference ΔT between this thermocouple and a second, uncoated, thermocouple. (On a third, potassium chloride-coated thermocouple $\Delta T = 0$, showing that the temperature rise on ZnO, Cr₂O₃ is not caused by recombination of OH radicals; cf. Smith.⁹⁵) A temperature rise ΔT is observed only for mixtures at pressures within the explosion peninsula; and it is not due to surface interaction of molecular hydrogen and oxygen. Total pressures up to 5 mm. were used, at temperatures of 476—693°. The maximum observed value for ΔT was 284°, with total pressure, $p = 3.83$ mm. From a consideration of the heat balance, the expression $\Delta T = 1000p_{\text{H}}/p$ is deduced theoretically, which would give $p_{\text{H}} = 1$ mm. It is found experimentally that $p_{\text{H}}/p \propto \Delta T$, when p_{H}/p is calculated from the kinetic expressions, with the proportionality constant 3000, so that the theoretical expression gives the correct order of magnitude for the hydrogen-atom concentration.

¹⁰⁸ Cf. A. G. Gaydon, "Spectroscopy and Combustion Theory," 2nd edn., London, 1948, p. 115.

¹⁰⁹ *Acta Physicochim. U.R.S.S.*, 1937, **7**, 567.

¹¹⁰ *J. Chem. Physics*, 1938, **6**, 439, 779; 1939, **7**, 485.

¹¹¹ *Acta Physicochim. U.R.S.S.*, 1942, **17**, 197.

¹¹² V. N. Kondratév, *J. Physical Chem. Russia*, 1946, **20**, 1231; *Compt. rend. Acad. Sci. U.R.S.S.*, 1944, **44**, 20.

¹¹³ *Physical Rev.*, 1940, **58**, 1121.

¹¹⁴ V. N. Kondratév and E. I. Kondratéva, *ibid.*, 1946, **51**, 607; *J. Physical Chem. Russia*, 1946, **20**, 1239; H. Kondratéva and V. N. Kondratév, *Acta Physicochim. U.R.S.S.*, 1946, **21**, 1, 629.

Sir A. C. Egerton and G. J. Minkoff¹¹⁵ have detected considerable amounts of hydrogen peroxide in hydrogen-oxygen flames (at 30–40 mm.) directed against a surface held at -180° . Part of the hydrogen peroxide is formed in the gas phase, and the mechanism $\text{H} + \text{O}_2 \rightarrow \text{HO}_2^*$; $\text{HO}_2^* + \text{H}_2 = \text{H}_2\text{O}_2 + \text{H}$ is suggested for its formation, an excited HO_2 radical being produced in *binary* collision between H and O_2 .

The evidence for the existence of the HO_2 radical in the gas phase has been reviewed by Minkoff,¹¹⁶ who applies the "semi-empirical" transition-state method to the reaction $\text{H} + \text{O}_2 = \text{HO} + \text{O}$.

Rates of elementary reactions. The following estimates are derived by Semenov and his collaborators (units : l. sec.⁻¹) :

- (a) $\text{H}_2 + \text{O}_2 = 2\text{OH}$; $k = 2.46 \times 10^{-12} T^{\frac{1}{2}} e^{-45,000/RT}$
- (b) $\text{OH} + \text{H}_2 = \text{H}_2\text{O} + \text{H}$; $k = 7 \times 10^{-12} T^{\frac{1}{2}} e^{-10,000/RT}$
- (c) $\text{H} + \text{O}_2 = \text{OH} + \text{O}$; $k = 6.4 \times 10^{-12} T^{\frac{1}{2}} e^{-18,000/RT}$
- (d) $^{117} \text{O} + \text{H}_2 = \text{OH} + \text{H}$; $k \leq 3 \times 10^{-11} T^{\frac{1}{2}} e^{-6,000/RT}$

For (c), Nalbandyan and Shubina⁹⁴ find $E = 17,800$ cal. from observations on the first limit, in agreement with observations on the second limit. Von Elbe and Lewis⁹⁹ give $E = 45.5$ and 17.0 kcal., respectively, for reactions (a) and (c).

For recent work on the influence of nitrogen dioxide upon the hydrogen-oxygen reaction, see F. S. Dainton and R. G. W. Norrish¹¹⁸ and A. B. Nalbandyan.¹¹⁹

The Hydrogen Sulphide-Oxygen Reaction.—The oxidation of hydrogen sulphide¹²⁰ takes place according to the equation $2\text{H}_2\text{S} + 3\text{O}_2 = 2\text{SO}_2 + 2\text{H}_2\text{O}$. The kinetics of the reaction have been comprehensively investigated by N. M. Emanuel.¹²¹ Over a wide range of pressure and temperature oxidation proceeds at a measurable speed. At sufficiently high pressures and temperatures thermal explosions occur. At low pressures and high temperatures, explosions occur between pressure limits. The reaction clearly shows the characteristics of branching chains.

The phenomenon of the induction period has been ingeniously investigated.¹²² The experimental arrangement included three interconnected

¹¹⁵ *Proc. Roy. Soc.*, 1947, **A**, **191**, 145; cf. W. H. Rodebush, C. R. Keizer, F. S. McKee, and J. V. Quaglino, *J. Amer. Chem. Soc.*, 1947, **69**, 538; E. J. Badin, *ibid.*, 1948, **70**, 3651.

¹¹⁶ Faraday Soc. Discussion, 1947, **2**, 151.

¹¹⁷ P. Harteck and U. Kopsch, *Z. physikal. Chem.*, 1931, **B**, **12**, 327.

¹¹⁸ *Proc. Roy. Soc.*, 1940, **A**, **177**, 445.

¹¹⁹ *J. Physical Chem. Russia*, 1946, **20**, 1283.

¹²⁰ Cf. L. Farkas, *Z. Elektrochem.*, 1931, **37**, 670; H. W. Thompson and N. S. Kelland, *J.*, 1931, 1809; B. Yakovlev and P. Shantarovich, *Acta Physicochim. U.R.S.S.*, 1937, **6**, 71.

¹²¹ *J. Physical Chem. Russia*, 1940, **14**, 863; *Acta Physicochim. U.R.S.S.*, 1944, **19**, 360.

¹²² N. M. Emanuel, *J. Physical Chem. Russia*, 1945, **19**, 15; cf. Semenov, *J. Chem. Physics*, 1939, **7**, 683; Semenov and Emanuel, *Compt. rend. Acad. Sci. U.R.S.S.*, 1940, **28**, 219.

cylindrical vessels, the "preparatory" vessel (1), the "intermediary" vessel (R), and the "indicator" vessel (2). Mixtures of hydrogen sulphide and oxygen, generally at an initial pressure (P_0) of 100 mm. were assembled in vessel (1) (kept generally at 270°). After a known time (t_1) in vessel (1), the reaction mixture was transferred to vessel (2) (kept generally at a higher temperature, *e.g.*, 300°), either directly or after a sojourn (t') in (R). Let τ_1° be the normal induction period for a reaction mixture with the initial conditions prevailing in vessel (1), and τ_2° that for the temperature of vessel (2) and for a freshly prepared reaction mixture at an initial pressure equal to that taken up by the experimental mixture when transferred to vessel (2). Let the observed induction period in (2) be τ_2 . Then, for example, with (1) at 270° and with $P_0 = 100$ mm., $\tau_1^\circ \sim 27$ secs. After direct transfer of reaction mixture from vessel (1) to vessel (2) (which was at 300°) the pressure (P) in (2) was 83 mm. In a series of experiments, it was then found that when $t_1 = \tau_1^\circ \sim 27$ secs., $\tau_2 = 0$, *i.e.*, reaction in (2) proceeded immediately with kinetics corresponding to the new temperature and pressure. Thus, active centres formed during the induction period in (1) survive the transfer to (2). With $t_1 < \tau_1^\circ$ then $\tau_2 < \tau_2^\circ$ and τ_2 is smaller the nearer t_1 is to τ_1° ; τ_2 approaches τ_2° as $t_1 \rightarrow 0$, corresponding to the immediate transfer from (1) to (2) of an "unprepared" reaction mixture.

The behaviour of the active centre was examined quantitatively by making use of the intermediary vessel (R). After a preparatory period of $t_1 \leq \tau_1^\circ$ in vessel (1), the mixture was kept for time t' in R , at room temperature. On connection with the indicator vessel (2), the pressure in the latter was approx. 50 mm., corresponding to $\tau_2^\circ \sim 60$ secs. In these circumstances the observed induction period τ_2 in vessel (2) was a linear function of t_1 . This result is in accord with Semenov's theory; for (with η = fractional pressure change) in (1) $\eta = A_1 e^{\phi_1 t_1}$ and, after transfer to (2) at time t_1 , $\eta = A_2 e^{\phi_2 t_1}$. Assuming no change during transfer, $A_1 e^{\phi_1 t_1} = A_2 e^{\phi_2 t_1}$ and $\tau_2 = \phi_1 t_1 / \phi_2 + (1/\phi_2) \ln A_1/A_2$.

With $t_1 = \tau_1^\circ$, and with vessel R at different temperatures (always less than that required to bring about the oxidation of hydrogen sulphide), the life of the active centre was found to be about 8 hours at room temperature and about 8 mins. at 135° , as indicated by the observation $\tau_2 \rightarrow \tau_2^\circ$. At all temperatures of R , τ_2 was a linear function of t' , the period of sojourn in R .

Defining the "relative concentration," c , of the active centre by putting $c = 1$ for $t_1 = \tau_1^\circ$, the relation between τ_2 and c was determined, by transferring a "prepared" mixture to R after a time t_1 spent in (1), and then replacing a known fraction of the mixture in R by an "unprepared" one from (1), and measuring τ_2 . The relation found is $\log c$ proportional to τ_2 , which is itself linear with t_1 . This exponential growth of the active centre with time is one of the first direct experimental proofs of Semenov's theory.

The destruction of the active centre (SO, see below) in R is of first order, with an activation energy of 8.5 kcal./mole. Water vapour (and also adjacent tap grease) accelerates its destruction. After a series of experiments a deposit of sulphur was found on the walls of R .

Sulphur monoxide. The active centre has been identified as sulphur monoxide, SO, previously suggested by Semenov as an intermediate in the oxidation of carbon disulphide and of carbon oxysulphide,¹²³ and detected spectroscopically¹²⁴ (along with CS) in a carbon disulphide flame. Sulphur monoxide was investigated particularly by P. W. Schenk,¹²⁵ who prepared it by the action of an electric discharge upon a mixture of sulphur and sulphur dioxide vapours, and assigned to it bands in the spectral region λ 2490—3400 Å. Schenk found sulphur monoxide to be stable for a considerable time at low pressure, then the characteristic bands vanished after 48 hours, giving place to bands of sulphur dioxide. The decomposition was written: $2\text{SO} = \text{SO}_2 + \text{S}$. In the gas phase, sulphur monoxide is largely present as the dimer S_2O_2 .^{125, 126}

The spectrum of sulphur monoxide has been identified in a reacting mixture of hydrogen sulphide and oxygen.¹²⁷ In further experiments by N. M. Emanuel,¹²² the indicator vessel (2), of the previous apparatus, was replaced by an absorption tube for the spectroscopic observations. The partial pressure of sulphur monoxide, P_{SO} , was estimated from the relative intensities of the absorption bands, calibrated by measurement of the pressure of sulphur dioxide formed by decomposition of sulphur monoxide.

The concentration of sulphur monoxide was found to grow during the induction period. With a stoichiometric mixture, $P_0 = 100$ mm. at 270° , the maximum value of P_{SO} was approx. 7.5 mm. at an extent of conversion (as indicated by pressure change) of $\eta = 0.18$. The maximum rate of reaction occurred at $\eta = 0.13$. Thus, in the initial stage of the oxidation of hydrogen sulphide, up to 20% of the latter was converted into sulphur monoxide. The spectroscopic measurements of P_{SO} fell on the kinetic curve for increase in the concentration of the active centre.

The decomposition of sulphur monoxide was followed spectroscopically in the intermediary vessel *R* at various temperatures. The spectroscopic results agreed with the previous kinetic results for the decay of the active centre and gave an activation energy of 8 kcal. (cf. kinetic value). The interaction of sulphur monoxide (formed in the preparatory vessel) with water, in the intermediary vessel, at 0 — 40° , was also examined spectroscopically. The rate of reaction decreased with rising temperature and was given by $-dc/dt = kc^{3/2}\gamma$, in which c and γ are (dimensionless) relative concentrations of sulphur monoxide and water vapour respectively. The reaction $\text{SO} + \text{S}_2\text{O}_2 + \text{H}_2\text{O} = \text{H}_2\text{S} + 2\text{SO}_2$ was proposed in interpretation of the result.

The identification of sulphur monoxide as the active centre was finally

¹²³ Cf. V. N. Kondratyev, *Acta Physicochim. U.R.S.S.*, 1942, **16**, 272.

¹²⁴ *Idem*, *Z. Physik*, 1930, **63**, 322.

¹²⁵ *Z. anorg. Chem.*, 1933, **211**, 150; P. W. Schenk and H. Platz, *ibid.*, 1935, **222**, 177.

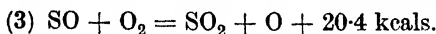
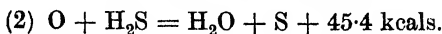
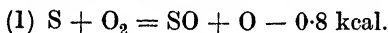
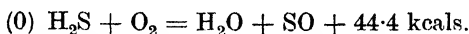
¹²⁶ E. I. Kondratyeva and V. N. Kondratyev, *J. Physical Chem. Russia*, 1940, **14**, 1528; V. G. Markovich and N. M. Emanuel, *ibid.*, 1947, **21**, 1251.

¹²⁷ N. M. Emanuel, D. S. Pavlov, and N. N. Semenov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1940, **28**, 618; *Bull. Acad. Sci. U.R.S.S., Cl. Sci. Chim.*, 1942, 98.

confirmed by the introduction of synthetic sulphur monoxide¹²⁸ (made by the method of Schenk) into stoichiometric mixtures of hydrogen sulphide and oxygen. With various proportions of added sulphur monoxide (estimated spectroscopically), the induction period was reduced to an extent which was in accord with the reduction caused by similar proportions of the active centre, formed in the preparatory vessel, as deduced from the kinetic experiments. The influence of synthetic sulphur monoxide upon the induction period of the explosive reaction (see below) and upon the values of the explosion limits was also in satisfactory quantitative agreement with that deduced for the active centre formed in the preparatory vessel. Synthetic sulphur monoxide enters into an explosive reaction with oxygen.¹²⁹ A lower pressure limit has been observed.

The explosive reaction. This has been studied¹³⁰ by arranging for the transferred gas in the "indicator" vessel (e.g., at 347°) to be at pressures (e.g., 14 mm.) lying within the explosion peninsula, after sojourn in the "preparatory" vessel at 270°, with $P_0 = 100$ mm. An induction period normally precedes explosion. It is again found that for $t_1 \leq \tau_1^\circ$, τ_2 for explosion is a linear function of t_1 , approaching zero as $t_1 \rightarrow \tau_1^\circ$. With $t_1 > \tau_1^\circ$ explosion occurs in the "indicator" vessel without an induction period, and will now take place at pressures which lie *outside* the normal explosion peninsula. For the increment ΔP_2 of the second limit pressure in the "indicator" vessel, it is found that $\Delta P_2 = \alpha P_{SO}$ and that $P_{SO} = \beta P_0$, where α and β are constant at a given temperature. These relations are not observed at the third (thermal) explosion limit.

For the mechanism of the reaction, the following scheme is put forward (author's numbering of equations) :



S and O deactivated at wall.

The step (4) is introduced because the maximum velocity occurs at an early stage (at 18–20% conversion) of the reaction.¹⁰⁵

Emanuel¹³¹ has studied the "intermediates" formed in chain reactions by a novel "contraction" method. The reaction is arrested by expanding the reaction mixture from the hot reaction vessel into a cold evacuated vessel (or by removing the heat source, with subsequent rapid or slow

¹²⁸ N. M. Emanuel, *Compt. rend. Acad. Sci. U.R.S.S.*, 1942, **36**, 145.

¹²⁹ H. Kondratyeva and V. N. Kondratyev, *ibid.*, 1941, **31**, 128; E. Kondratyeva and V. Kondratyev, *J. Physical Chem. Russia*, 1941, **15**, 731; 1944, **18**, 102.

¹³⁰ Emanuel, *Compt. rend. Acad. Sci. U.R.S.S.*, 1942, **35**, 250.

¹³¹ *Ibid.*, 1945, **48**, 488; 1948, **59**, 1137; V. G. Markovich and N. M. Emanuel, *J. Physical Chem. Russia*, 1947, **21**, 1259.

cooling). The contraction Δ (due to recombination of radical "intermediates" or sometimes to association of end products) is determined as the difference between the pressure exerted in the cold vessel by the cooled reaction mixture and that exerted by dry air under the same conditions. Contractions have been observed during the oxidation of hydrogen sulphide, acetaldehyde, propylene, and acetylene. For hydrogen sulphide, Δ changes regularly as the reaction proceeds, going through a maximum at 20% conversion. It is found that $\Delta \propto [\text{SO}]$; and that the dependence of Δ on temperature of the reaction mixture agrees with the temperature effect of $[\text{SO}]$, calculated from the influence of $[\text{SO}]$ on the ignition limit.

Additional papers on the mathematical theory of chain reactions are those of N. N. Semenov,¹³² A. A. Frank-Kamenetsky,¹³³ N. S. Akulov,¹³⁴ and L. von Muffling.¹³⁵

K. S.

G. W.

F. S. DANTON.

G. S. HARTLEY.

K. SINGER.

G. WILLIAMS.

¹³² *J. Physical Chem. Russia*, 1943, **17**, 187; *Acta Physicochim. U.R.S.S.*, 1943, **18**, 93.

¹³³ *Ibid.*, 1942, **16**, 357.

¹³⁴ *E.g., Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **48**, 644.

¹³⁵ *Z. Physik*, 1944, **122**, 787.

INORGANIC CHEMISTRY.

For some years past these Reports have taken the form of brief articles on special topics. The departure this year implies no criticism of this policy and is conditioned solely by the available material, which it is felt demands a broad survey of the whole gamut of Inorganic Chemistry. Hence, after dealing with some general matters, this Report picks out what appears of most interest in a review based on the Periodic Table.

Though the plea in these Reports¹ for an English-language journal for inorganic topics has so far gone unanswered, there have been nevertheless welcome additions to the reference library of the inorganic chemist,²⁻⁶ among them a second volume,³ edited by W. C. Fernelius, of "Inorganic Syntheses," and the first⁵ of seven projected volumes reviewing inorganic chemistry in Germany during the war years. The latter contains much valuable material, some of which has been referred to in these Reports, but also much which has not been previously published. For teachers, L. Pauling's⁶ approach to first-year chemistry will be found stimulating and inspiring.

There is little need to point out the lack of order in inorganic nomenclature, or to stress custom and prejudice as contributory causes. The I.U.C. nomenclature committee issued no report after the London meeting in 1947 and the results of the forthcoming Amsterdam meeting are awaited with interest.⁷ Inadequacies in previous recommendations have been discussed by Fernelius⁸ and by (Miss) J. D. Scott⁹ and co-ordination compounds have been specifically examined.¹⁰ But of greater value to those who seek to conform to prescribed practice is A. D. Mitchell's monograph "British Chemical Nomenclature."¹¹ Here the assist-

¹ *Ann. Reports*, 1944, **41**, 87.

² R. W. G. Wyckoff, "Crystal Structures," Interscience, 1948; D. M. Yost and H. Russell, "Systematic Inorganic Chemistry," O.U.P., 1946; E. B. Maxted, "Modern Advances in Inorganic Chemistry," O.U.P., 1947.

³ "Inorganic Syntheses," Vol. II, McGraw-Hill, 1946.

⁴ W. H. Keesom, "Helium," Elsevier Publishing Co., 1942; J. Dement and H. C. Drake, "Rarer Metals," Chemical Publishing Co., N.Y., 1946; J. G. F. Druce, "Rhenium," C.U.P., 1948; D. M. Yost, H. Russell, and C. S. Garner, "Rare Earth Metals and their Uses," Chapman & Hall, 1947.

⁵ FIAT Review of German Science (1939-1946), Inorganic Chemistry, Vol. I, 1948.

⁶ "General Chemistry," W. H. Freeman, California, 1947.

⁷ We are indebted to Professor Bassett for acquainting us with the position and providing us with the draft of "Inorganic Chemical Nomenclature," being suggestions put forward by himself and (the late) R. V. G. Ewens.

⁸ W. C. Fernelius, *Chem. Eng. News*, 1948, **26**, 161.

⁹ *Chem. Reviews*, 1943, **32**, 73, and ref. (3), Appendix, p. 257.

¹⁰ W. C. Fernelius, E. M. Larson, L. E. March, and C. L. Rollinson, *Chem. Eng. News*, 1948, **26**, 520.

¹¹ "British Chemical Nomenclature," Edward Arnold, 1948.

ant editor of the Chemical Society, though not writing in an official capacity, sets out in a handy reference volume the conventions adopted by the *Journal*, at the same time indicating other usages, notably those recommended in the I.U.C. (1940) rules and those adopted in *Chemical Abstracts*. Recommendations for the naming of oxy-acids, of peroxy-acids as distinct from per-acids, of iso- and hetero-polyacids, of the hydrides of boron, silicon, and the elements of Group IVB may be selected as ones where agreement is fairly general or where general adoption is likely to be only a matter of time. On the other hand, the indication of variable metallic valency in oxides, salts, and complex compounds is still under consideration. The terminations *-ous* and *-ic* are obviously unsatisfactory—where an element exhibits more than two valencies, where the same termination does not indicate the same numerical valency in two different metals, and where, in some co-ordination compounds, the valency of the metal is by no means certain. It seems desirable to retain the Stock method of indicating valency for single oxides and salts [Roman numerals in parentheses after the metal, *e.g.*, lead(IV) oxide, PbO_2 ; iron(II, III) oxide, Fe_3O_4 ; copper(I) chloride, CuCl]. The Stock method is applicable to co-ordination compounds {hexacyanoferrate(II) ion for $[\text{Fe}(\text{CN})_6]^{4-}$, molybdenum(III) oxopentathiocyanatomolybdate(VI) for $\text{Mo}[\text{Mo}(\text{CNS})_5\text{O}]_3$ } though open to the same objection that the valency on the central atom is not always known. An alternative proposal due to (the late) R. V. G. Ewens is that the charge on the ion be placed in Arabic numerals in parentheses after the name: thus, hexacyanoferrate(−4), and molybdenum(+3) oxopentathiocyanatomolybdate(−1), for the above examples. Without prejudice to any recommendations that may be made by the next I.U.C. Committee the Ewens method has been used in this Report in conjunction with the Stock method to give chemists an opportunity to assess their merits.

For the remaining unnamed element 61, *prometheum*, Pm, has been suggested,¹² supported by detailed evidence of priority. That many inorganic chemists have seen their own version of the Periodic Table is evident from the number that have appeared,¹³ among them a further *Helix Chemica*,¹⁴ a plot of atomic mass against number of electrons in incomplete shells by T. Grjébine,¹⁵ and a less ambitious but very workable contribution by T. S. Wheeler.¹⁶ The concept of chemical element has been studied,¹⁷ and its development traced¹⁸ from its earliest beginnings to our present knowledge of the isotopic nature of the elements. Isotopic abundance rules have been examined^{19, 20} and attempts have been made

¹² J. A. Marinsky and L. E. Glendenin, *Chem. Eng. News*, 1948, **26**, 2346.

¹³ W. Finke, *Z. Physik*, 1944, **122**, 230; P. C. Banerjee, *J. Indian Chem. Soc.*, 1945, **22**, 130; Y. Ta, *Ann. Physique*, 1946, **1**, 88.

¹⁴ J. Cueileron, *Compt. rend.*, 1946, **222**, 742.

¹⁵ *Bull. Soc. chim.*, 1948, 473.

¹⁶ *Chem. and Ind.*, 1947, **42**, 638.

¹⁷ R. Hooykaas, *Chem. Weekblad*, 1947, **43**, 526.

¹⁸ N. Feather, *Proc. Roy. Soc. Edin.*, 1944—6, **62**, 211.

¹⁹ H. E. Suess, *Z. Naturforsch.*, 1947, **2a**, 311.

²⁰ F. C. Frank, *Proc. Physical Soc.*, 1947, **60**, 211.

to correlate mass and charge regularities with β -activity, and relative abundance with susceptibility to nuclear fission.¹⁸ The chemistry and physics of isotopic indicators have been reviewed:²¹ in this connection reference to some particular elements is made below. Questions of valency and structural chemistry have received considerable attention in previous Reports and elsewhere and have therefore been largely omitted this year, but reference must be made to reviews by Pauling of some of the problems²² and to his recent exposition²³ of the metallic bond. Among other matters of general interest, the state and properties of metallic surfaces,²⁴ partition chromatography²⁵ in inorganic chemistry, and a list²⁶ of declassified atomic energy reports may be mentioned.

There seems to be general agreement^{27, 28, 29} that the stability of complexes of bivalent ions (with ammonia, ethylenediamine, propylenediamine, salicylaldehyde, salicylaldehyde-5-sulphonate, *O*-formylnaphthols, glycine, oxine) follows an order which is independent of the nature of the ligands :



but no simple relation exists between stability and covalent radii, and much remains to be learnt about chelate binding. In continuation of work already reported³⁰ on the stability of copper chelate compounds, M. Calvin and R. H. Bailes³¹ have studied the polarographic reduction of a number of such complexes dissolved in 50% (by volume) aqueous pyridine. Most of the chelated copper(I) compounds were unstable and dissociated to give the $[\text{Cu}(\text{C}_5\text{H}_5\text{N})]^+$ ion, though it was found, as might be expected, that the linking of co-ordinating groups together led to an increased stability. It has also been shown³² that there is complete correlation between stability and the rate of exchange of copper chelate compounds with copper(II) acetate in pyridine solution. The stability of complexes with the tridentate nitrilotriacetic acid, $\text{N}(\text{CH}_2\text{CO}_2\text{H})_3$, does, however, show³³ a decrease with increasing radius where the central atoms are Li, Na, Ca, Sr, Ba. In

²¹ P. Süe, *J. Chim. physique*, 1941, **38**, 31; G. de Hevesy, *Finska Kem. Medd.*, 1946, **55**, 55.

²² *Chem. Eng. News*, 1947, **25**, 2970, 3045; *J.*, 1948, 1461.

²³ *Nature*, 1948, **161**, 1019; *J. Amer. Chem. Soc.*, 1947, **69**, 542; L. Pauling and F. J. Ewing, *Rev. Mod. Physics*, 1948, **20**, 112.

²⁴ C. H. Desch, *Nature*, 1946, **157**, 271.

²⁵ T. V. Arden, F. H. Burstall, G. R. Davies, J. A. Lewis, and R. P. Linstead, *Nature*, 1948, **162**, 691.

²⁶ *Nature*, 1947, **159**, 411; 1947, **160**, 445; 1948, **161**, 146; M. C. Leikend, *Bulletin of Atomic Scientists*, 1947, 127.

²⁷ H. M. N. H. Irving and R. J. P. Williams, *Nature*, 1948, **162**, 746.

²⁸ D. P. Mellor and L. Maley, *ibid.*, 1947, **159**, 370; 1948, **161**, 436.

²⁹ M. Calvin and N. C. Melchior, *J. Amer. Chem. Soc.*, 1948, **70**, 3270, 3273.

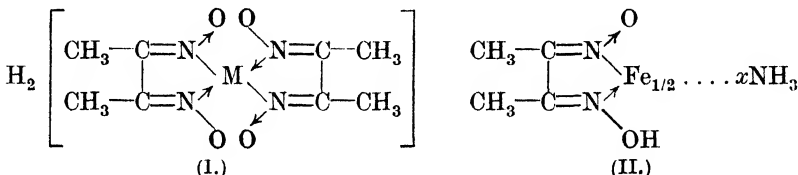
³⁰ *Ann. Reports*, 1945, **42**, 70.

³¹ *J. Amer. Chem. Soc.*, 1946, **68**, 949.

³² R. B. Duffield and M. Calvin, *ibid.*, p. 557.

³³ G. Schwarzenbach, E. Kampitsch, and R. Steiner, *Helv. Chim. Acta*, 1945, **28**, 828.

demonstration of formula (I) for dimethylglyoxime complexes F. Feigl and H. S. Suter³⁴ have prepared several salts of the acid (I), where $M = Pd$, and have shown that the acid gives no precipitate in the presence of nickel ions. The inferred absence of free dimethylglyoxime indicates that (I) is a true inner complex and suggests that the complex, formerly written as (II), is in fact the ammonium salt of (I), where now $M = Fe$:



Other papers describe complex salts of ethanolamine with Th, Cr, Sn, Co, Cu, Ni;³⁵ phenoxides involving Be, Al, Ti, Th, Zr;³⁶ a dry method³⁷ of preparation of metal ammine salts, and a method³⁸ using carbonyl or thionyl chloride, for obtaining the anhydrous salts from hydrated Be, Al, Mg, Sr, Ba, Tl, Sn, Cr^{III}, Cu^{II}, Fe^{II}, Fe^{III}, Co, and Ni chlorides.

Group 0.—Thirty-one natural gases containing more than one volume % of helium have been examined ³⁹ as likely profitable sources, and E. Glückauf and F. A. Paneth ⁴⁰ have measured the helium content of the atmosphere up to 25 km., finding no variation greater than 0.2% at heights less than 20 km. No evidence for gravitational separation of the constituents of the atmosphere is afforded. A recent conference ⁴¹ on liquid helium has disclosed more manifestations of anomalous transport properties and a new kinetic theory thereby required. Superfluidity provides a new method ⁴² for separating helium isotopes of mass 3 and 4. Mass-spectrograph beams of neon ions can be absorbed ⁴³ on silver discs up to some 2 $\mu\text{g. cm.}^{-2}$ to provide convenient samples of spectroscopically clean "monotopic" neon. The pure isotope is released by heating the metals in a vacuum. Krypton and xenon have been examined ⁴⁴ for relative isotope abundance.

Group I.—The extension⁴⁵ of the Clusius–Dickel thermal diffusion method to the separation of ortho- and para-hydrogen is of great interest in that these species have identical molecular weight. A tube 1 m. long,

³⁴ *J.*, 1948, 378.

³⁵ H. Britzinger and B. Hesse, *Z. anorg. Chem.*, 1944, **252**, 293.

³⁶ H. Funk and E. Rogler, *ibid.*, p. 323.

³⁷ G. Jones and W. Juda, U.S. Pat., 2,412,890.

³⁸ H. Hecht, *Z. anorg. Chem.*, 1947, **254**, 37.

³⁹ F. P. Vajna, *Bányászati és Kőhászati Lapok*, 1942, **75**, 161.

⁴⁰ *Proc. Roy. Soc.*, 1946, **185**, A, 89.

⁴¹ K. Mendelssohn, *Nature*, 1947, 160, 385.

⁴² J. Franck, *Physical Rev.*, 1946, **70**, 561; J. G. Daunt, R. E. Probst, H. L. Johnston, L. T. Aldrich, and A. O. Nier, *ibid.*, 1947, **72**, 502.

⁴³ J. Koch, *Nature*, 1948, **161**, 566.

⁴⁴ M. Lounsbury S. Epstein, and H. G. Thode, *Physical Rev.*, 1947, 72, 517.

⁴⁵ K. Schafer and H. Corte, *Naturwiss.*, 1946, **33**, 92.

cooled externally to 80°K. and furnished with a coaxial wire maintained at 220°K. , gave an enrichment in $p\text{-H}_2$ of 4.8% at the lower end of the column when the original mixture was the normal $o\text{-H}_2$ 75% and $p\text{-H}_2$ 25%. A factor of about 14 has been obtained ⁴⁶ for protium-tritium separation at a platinum cathode in 10% sodium hydroxide. The states of hydrogen absorbed in, and desorbed from, palladium and other metals have been investigated.⁴⁷ An interesting description ⁴⁸ of the liquid-hydrogen plant at Oxford is available in the new journal *Research*. E. Wiberg ⁴⁹ has reviewed German contributions to the chemistry of hydrides.

Lithium has been compared ⁵⁰ with magnesium in standard Grignard reactions. A comparative essay ⁵¹ on sodium and potassium brings out small differences in their properties. They have been used as active reducing agents for halides of other metals, as witness the earliest manufacture of aluminium, and it now appears ⁵² that mixtures of many fluorides, chlorides, bromides, and iodides with these metals may be detonated by shock. Evidence has been adduced ⁵³ for the existence at 77°C. of unstable, and hitherto unreported, NaO_2 . A. Hérol ⁵⁴ has measured the dissociation pressure of potassium hydride, and H. Guiter ⁵⁵ has included lithium, sodium, and potassium carbonates in his extensive hydrolysis studies. A small glass Castner-Kellner cell has been described ⁵⁶ for the preparation of caesium and rubidium hydroxides. Four compounds CsF_nHF have been reported,⁵⁷ where $n = 1, 2, 3$, and 6.

Copper has received considerable attention. Its oxidation has been investigated ⁵⁸ by use of a thin deposited layer of radioactive, ^{64}Cu , tracer. The formula $\text{Cu}[\text{Cu}(\text{OH})_2]$ has been assigned ⁵⁹ to copper(I) hydroxide and a similar structure to copper(I) salts. Copper polysulphide and polysulphosalts have been investigated,⁶⁰ and diamagnetic Cu_2S_7 identified along with lower sulphides and salts $\text{K}_2\text{Cu}_3\text{S}_{10}$ and KCuS_4 . H. Guerin and R. Mas ⁶¹ describe four copper arsenates of which natural olivenite, $4\text{CuO} \cdot \text{As}_2\text{O}_5 \cdot \text{H}_2\text{O}$, is richest in copper and the only one stable in water. The addition of

⁴⁶ M. L. Eidinoff, *J. Amer. Chem. Soc.*, 1947, **69**, 2507.

⁴⁷ J. Bénard and P. Albert, *Compt. rend.*, 1947, **224**, 45; A. Portevin, *Metal Prog.*, 1946, **50**, 1206.

⁴⁸ G. O. Jones, A. H. Larsen, and F. E. Simon, *Research*, 1948, **1**, 420.

⁴⁹ Ref. 5, p. 125.

⁵⁰ Z. W. Wicks, *Interchem. Rev.*, 1946, **6**, 69.

⁵¹ H. N. Gilbert, *Chem. Eng. News*, 1948, **26**, 2604.

⁵² J. Cuéillon, *Bull. Soc. chim.*, 1945, **12**, 88.

⁵³ W. H. Schechter, H. H. Sisler, and J. Kleinberg, *J. Amer. Chem. Soc.*, 1948, **70**, 267.

⁵⁴ *Compt. rend.*, 1947, **224**, 1826.

⁵⁵ *Bull. Soc. chim.*, 1948, **15**, 26, 29, 31.

⁵⁶ A. F. Winslow, H. A. Liebafsky, and H. M. Smith, *J. Physical Coll. Chem.*, 1947, **51**, 967.

⁵⁷ R. Virginia Winsor and G. H. Cady, *J. Amer. Chem. Soc.*, 1948, **70**, 1500.

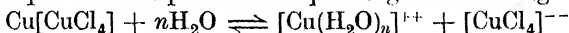
⁵⁸ J. Bardeen, W. H. Brattain, and W. Shockley, *J. Chem. Physics*, 1946, **14**, 714.

⁵⁹ E. Carrière and A. Raynaud, *Bull. Soc. chim.*, 1945, **12**, 920.

⁶⁰ G. Peyronel and (Signa.) E. Pacilli, *Gazzetta*, 1946, **76**, 265.

⁶¹ *Compt. rend.*, 1948, **226**, 1615; **227**, 973.

sodium hydroxide to copper(II) sulphate solutions results, according to pH measurements⁶² and examination of precipitates, in two basic sulphates, $4\text{CuO}\cdot\text{SO}_3$ and $10\text{CuO}\cdot\text{SO}_3$, before the formation of $\text{Cu}(\text{OH})_2$; the second is not, however, observed if the pH measurement is made some 5 hours after adding the reagent. Similarly, $4\text{CuO}\cdot\text{N}_2\text{O}_5$ or $5\text{CuO}\cdot\text{N}_2\text{O}_5\cdot 5\text{H}_2\text{O}$ and $3\text{CuO}\cdot\text{CuCl}_2\cdot\text{H}_2\text{O}$ have been observed. From activity, conductivity, and other measurements on aqueous copper(II) chloride, three types of solution are recognised,⁶³ green $[\text{CuCl}_4]^{--}$, blue $[\text{Cu}(\text{H}_2\text{O})_2]^{++}$, and colourless Cu_2Cl_4 . There are sharp transition points corresponding to the change



and on further dilution to the colourless solution.

The stabilities of dicarbonyl copper(I) chloride and bromide have been assessed⁶⁴ in terms of heat of formation, and a deduction from the Nernst equation has been made that, for stability, that quantity must be greater than 10.7 kcal. per mole of CO. Thus $\text{Cu}_2\text{Br}_2\cdot 2\text{CO}$ (10.0 kcal./CO mole) is unstable whereas $\text{Cu}_2\text{Cl}_2\cdot 2\text{CO}$ (11.0) is stable up to 307° K. In a further attempt to prepare copper carbonyl, H. Bloom⁶⁵ has passed carbon monoxide for several weeks over copper gauze kept at ~550° in a glass tube. A substantial copper mirror in the 250—400° zone is ascribed, in the absence of chlorine, to the formation and decomposition of copper carbonyl. F. Körösy,⁶⁶ in decomposing copper(II) formate at 200°, has observed a partially volatile compound which deposits a copper mirror on hot glass. A similar phenomenon was observed with silver formate, but not with formates of nickel, iron, cobalt, zinc, or cadmium or with copper oxalate or mesoxalate. Bloom's mirror formation is thus likely to be due in some manner to the presence of traces of hydrogen-containing compounds in the carbon monoxide. The solution of carbon monoxide in aqueous ammoniacal copper(I) chloride apparently consists⁶⁷ in physical solution, formation of two distinct complexes (one attacked by potassium cyanide, the other not), and oxidation to carbon dioxide by a process probably involving $2\text{Cu}^+ \rightarrow \text{Cu}^{++} + \text{Cu}^0$ (metal) and $2\text{Cu}^{++} + \text{CO} + \text{H}_2\text{O} \rightarrow 2\text{Cu}^+ + 2\text{H}^+ + \text{CO}_2$. Spectrographic investigation⁶⁸ of copper(I), silver, mercury(II), and potassium cyanides suggests that CuCN and AgCN exist as internal complexes and that it is this fact, rather than cyanide-isocyanide isomerism, which accounts for the formation of carbylamine from copper(I) and silver cyanides whereas those of potassium and mercury(II) yield cyanides by alkylation. Acetates,⁶⁹ phenylacetates,⁷⁰ and ethylenediamine complexes of pyrophosphates⁷¹ have been studied. In connection with the latter, a formula of the

⁶² E. Carrière, H. Guiter, and E. Portal, *Bull. Soc. chim.*, 1946, **13**, 396.

⁶³ C. Gomez Herrera, *Anal. Fis. Quím.*, 1946, **42**, 165.

⁶⁴ B. Ormont, *Acta Physicochim. U.R.S.S.*, 1946, **21**, 741.

⁶⁵ *Nature*, 1947, **159**, 539.

⁶⁶ *Ibid.*, 1947, **160**, 21.

⁶⁷ R. Duguet, *Compt. rend.*, 1948, **226**, 1527.

⁶⁸ F. Gallais, *Bull. Soc. chim.*, 1945, **12**, 657.

⁶⁹ (Mlle.) M. Gerbault, *Compt. rend.*, 1946, **222**, 292.

⁷⁰ M. Crawford, *Nature*, 1947, **160**, 19.

⁷¹ P. McCutcheon and S. Raymond, *J. Amer. Chem. Soc.*, 1947, **69**, 276.

type $[\text{Cu}, 2\text{en}][\text{CuP}_2\text{O}_7]$ has been advanced on the basis of reactions with silver nitrate and potassium thiocyanate solutions. Compounds $\text{Cu}_2\text{P}_2\text{O}_7 \cdot 2\text{en} \cdot 2\text{H}_2\text{O}$ (dark blue), $\text{Cu}_2\text{P}_2\text{O}_7 \cdot 3\text{en} \cdot 6\text{H}_2\text{O}$ (lustrous blue plates, $\text{Cu}_2\text{P}_2\text{O}_7 \cdot 4\text{en} \cdot 6\text{H}_2\text{O}$, and one copper-zinc compound $\text{CuZnP}_2\text{O}_7 \cdot 2\text{en} \cdot 2\text{H}_2\text{O}$ (both purple needles) are described. The last compound is prepared by adding zinc pyrophosphate to a solution of $\text{Cu}_2\text{P}_2\text{O}_7 \cdot 4\text{en} \cdot 6\text{H}_2\text{O}$. Presumably the suggested anion retains its identity in this mixed compound, in view of the similarity of colour. F. Gallais and J. P. Vives ⁷² have found that thermal decomposition of tetramminocopper(+2) nitrite does not lead to copper(II) nitrite but to copper oxide and nitrate with the single possible intermediate diamminodinitrocopper. In aqueous solution hydrated copper(II) nitrite exists as $[\text{Cu}(\text{NO}_2)(\text{H}_2\text{O})_3]^+$, and with excess of nitrite, $[\text{Cu}(\text{NO}_2)_2(\text{H}_2\text{O})_2]$ and $[\text{Cu}(\text{NO}_2)_3(\text{H}_2\text{O})]^-$ may be present. Dissociation pressures of pyridinocopper(+2) perchlorate have been measured.⁷³ J. G. Breckenridge ⁷⁴ has prepared tridentate chelate complexes of copper(II) and nickel(II) involving $\text{NH}_2 \cdot [\text{CH}_2]_2 \cdot \text{NH} \cdot [\text{CH}_2]_2 \cdot \text{NH}_2$ and $\text{OH} \cdot [\text{CH}_2]_2 \cdot \text{NH} \cdot [\text{CH}_2]_2 \cdot \text{NH}_2$.

Active silver oxides may be prepared ⁷⁵ by the action of alkaline potassium peroxydisulphate, $\text{K}_2\text{S}_2\text{O}_8$, on silver nitrate solution in the presence of bivalent manganese, copper, and cobalt nitrates. The washed precipitate contains some base-metal oxide and is improved as an oxidant for carbon monoxide by the presence of 0.1–0.8% of MnO , or CuO , or CoO , of which the first gives the greatest increase in activity with the least decrease in stability. The activated AgO is suitable for gas masks. Silver acetylides of the form Ag_2C_2 , AgNO_3 and $\text{Ag}_2\text{C}_2 \cdot 6\text{AgNO}_3$ have been respectively prepared ⁷⁶ directly from 10% and 25% silver nitrate solutions and have been characterised. The decomposition of single crystals of silver oxalate at 100–140° has been followed ⁷⁷ by X-ray diffraction analysis, from which it appears that the monoclinic structure is maintained until all the $\text{Ag}_2\text{C}_2\text{O}_4$ had disappeared. Part of the silver released assumed preferred orientations, the ratio of orientated to unorientated metal remaining constant throughout the decomposition. The gas evolution in both the photolytic and the thermal decomposition has also been measured ⁷⁸ and correlated with the three-dimensional growth of silver centres. Only two species, Ag_2CrO_4 and $\text{Ag}_2\text{Cr}_2\text{O}_7$, have been detected ⁷⁹ in the three-component system $\text{Ag}_2\text{O}-\text{CrO}_3-\text{H}_2\text{O}$ at 30°. (In the same paper copper chromates are also mentioned.)

Gold is precipitated ⁸⁰ quantitatively from trichloride solutions by the action of hydrogen peroxide or sodium chlorite. Chlorine is evolved if

⁷² *Bull. Soc. chim.*, 1948, **15**, 702.

⁷³ P. C. Sinha and R. C. Ray, *Trans. Faraday Soc.*, 1948, **44**, 790.

⁷⁴ *Canadian J. Res.*, 1948, **25B**, 11.

⁷⁵ J. H. de Boer and J. van Ormondt, B.P. 579,809, 579,817.

⁷⁶ J. A. Shaw and E. Fisher, *J. Amer. Chem. Soc.*, 1946, **68**, 2745.

⁷⁷ R. L. Griffith, *J. Chem. Physics*, 1946, **14**, 408.

⁷⁸ F. C. Tompkins, *Trans. Faraday Soc.*, 1948, **44**, 206.

⁷⁹ A. N. Campbell and H. P. Lemaire, *Canadian J. Res.*, 1947, **25B**, 243.

⁸⁰ O. Erämettä, *Suomen Kem.*, 1942, **15B**, 11.

platinum and allied metals are not precipitated. X-Ray study has revealed ⁸¹ the isomorphism of hexachloroaurates(—3), $\text{Cs}_4\text{M}^{\text{II}}[\text{AuCl}_6]_2$, where $\text{M}^{\text{II}} = \text{Cu, Zn, Hg, Cd}$ (the cadmium compound being new), with compounds of type $\text{Cs}_2\text{AgAuCl}_6$ and $\text{Cs}_2\text{Au}^{\text{I}}\text{Au}^{\text{III}}\text{Cl}_6$, CsCdCl_3 , Cs_2HgCl_3 ; the last two should therefore be formulated as $\text{Cs}_2\text{M}_2\text{Cl}_6$. M. A. Peacock and R. M. Thompson ⁸² have described a new mineral, gold telluride Au_2Te_3 .

Group II.—Work on beryllium seems to be mainly confined to that of H. N. Terem, who has applied the method of continuous differential weighing to the dissociation of basic beryllium carbonate, ⁸³ $\text{BeCO}_3 \cdot 5\text{Be}(\text{OH})_2 \cdot 3\text{H}_2\text{O}$, of beryllium nitrate, ⁸⁴ and of beryllium sulphate. ⁸⁵ Activation energies are given. The carbonate is apparently a mixture of BeCO_3 and $\text{Be}(\text{OH})_2$ and no evidence was found for a basic sulphate intermediate. The preparation of beryllium sulphide by the action of carbon disulphide vapour diluted with nitrogen on heated beryllium oxide has been described. ⁸⁶

The formation of magnesium carbides, MgC_2 and Mg_2C_3 , ⁸⁷ and of magnesium sulphide ⁸⁸ has been shown to occur when acetylene, pentane, and hydrogen sulphide respectively are passed over heated magnesium. Anhydrous magnesium chloride results ⁸⁹ from heating the hydrated chloride or the oxide with ammonium chloride above 350° . W. H. Hartford ⁹⁰ has prepared $\text{MgCr}_2\text{O}_7 \cdot 5\text{H}_2\text{O}$ as bright red-orange deliquescent crystals from MgO and CrO_3 in water with pH adjusted to 2.8—3.0. At 95.4° the compound yields a monohydrate which is stable up to 300° . A recent general account ⁹¹ of the preparation and industrial applications of calcium hydride is available. Indication ⁹² that calcium tetroxide contains O_2^- ions is gathered from the fact that preparations of calcium peroxide containing 5% of CaO_4 are paramagnetic. Chlorination ⁹³ of dry calcium hydroxide yields $\text{Ca}(\text{OH})\text{Cl} \cdot \text{H}_2\text{O}$, resistant to further attack. Slightly moist material, in the cold, gives $\text{Ca}(\text{OH})\text{Cl}$ and $\text{Ca}(\text{OH})\text{ClO} \cdot \text{H}_2\text{O}$, and, at 40° , the optimum temperature, $2\text{Ca}(\text{OH})\text{Cl} \cdot \text{Ca}(\text{ClO})\text{Cl} \cdot \text{Ca}(\text{OCl})_2 \cdot 3\text{H}_2\text{O}$, containing 41.3% of active Cl. Further chlorination is prevented by the inertness of the basic chloride. The thermal decomposition ⁹⁴ of calcium carbonate is perfectly reversible and is the only reversible part of the decomposition ⁹⁵ of dolomite. Both of biological and general interest is the

⁸¹ A. Ferrari, R. Cecconi, and L. Cavalea, *Gazzetta*, 1943, **73**, 23.

⁸² *Amer. Min.*, 1946, **31**, 515.

⁸³ H. N. Terem, *Compt. rend.*, 1946, **222**, 1436; *Rev. Fac. Sci. Istanbul*, 1946, **A**, 11, 107.

⁸⁴ *Idem, ibid.*, p. 99; *Compt. rend.*, 1946, **222**, 1387. ⁸⁵ *Idem, ibid.*, p. 1347.

⁸⁶ A. Chrétien and P. Silber, *ibid.*, 1948, **226**, 2072.

⁸⁷ F. Irrmann and W. D. Treadwell, *Helv. Chim. Acta*, 1947, **30**, 775.

⁸⁸ K. Nielsen, *Ann. Chim.*, 1947, **2**, 354.

⁸⁹ J. G. N. Gaskin, *J. Soc. Chem. Ind.*, 1946, **65**, 215.

⁹⁰ W. H. Hartford, *J. Amer. Chem. Soc.*, 1946, **68**, 2192.

⁹¹ E. E. Halls, *Ind. Chem.*, 1946, **22**, 680.

⁹² P. Ehrlich, *Z. anorg. Chem.*, 1944, **252**, 270.

⁹³ L. Forsén, *Svensk Kem. Tidskr.*, 1941, **53**, 217.

⁹⁴ L. Hackspill and (Mlle.) H. Ostertag, *Compt. rend.*, 1948, **227**, 1000.

⁹⁵ Y. Schwob, *Compt. rend.*, 1947, **224**, 47.

observation⁹⁶ that phosphate increases the solubility of calcium carbonate and bicarbonate and that of normal calcium phosphate, through the formation of the complexes $[\text{Ca}_2(\text{HPO}_4)(\text{CO}_3)]$ and $[\text{Ca}_2(\text{PO}_4)(\text{CO}_3)]^-$, but that bicarbonate does not correspondingly affect the solubility of magnesium hydrogen phosphate. Complex oxalato- and acetato-calcium chloride have been prepared⁹⁸ and calcium aluminate⁹⁹ and tetracalcium aluminoferrate¹ have been the subject of chemical, X-ray, and magnetic investigation.

Among the phases observed by X-ray study² in the system $\text{BaCO}_3\text{--Fe}_2\text{O}_3$, a perovskite-type phase $\text{Ba}_3\text{Fe}_8\text{O}_{21}$ (iron valency 3.25) is observed which lacks three oxide ions per unit cell for ideal structure. The defect is associated with catalytic activity in the oxidation of carbon monoxide. Hard, clear, pale yellow crystals of barium titanium oxide have been prepared³ and the transition point between tetragonal and cubic structure (between 122° and 129°) has been identified⁴ with the Curie point transition temperature ($\sim 125^\circ$) between ferro- and non-ferro-electric structures. The unusually high permittivity (ferroelectric) of the tetragonal variety of this perovskite-type compound is associated with the ability of the Ti^{4+} ion to "rattle" within its octahedral cage of oxide ions. Strontium hexanitritocobaltate(−3), $\text{Sr}_3[\text{Co}(\text{NO}_2)_6]_2 \cdot 15\text{H}_2\text{O}$, has been prepared⁵ from the silver salt and strontium chloride: the method is not applicable to calcium and cadmium salts.

Very pure zinc in 95% yield, free from ZnO, As, Fe, and Pb, can be obtained⁷ by reducing zinc sulphide, oxide or silicate with CaC_2 —strongly exothermal reactions, commencing at $700\text{--}800^\circ$, catalysed by sodium chloride, which may be carried out in an atmosphere of steam or in a vacuum. The oxide of zinc has been found⁸ to vaporise by way of Zn and O_2 , the heat of sublimation being $111\text{--}112.5$ kcal./mole of ZnO. A temperature of 1950° is required at 760 mm. Hydrolysis studies⁹ of zinc chloride and nitrate solutions on progressive dilution give evidence of $[\text{ZnX}(\text{OH})_3]^-$ and $\text{ZnX}(\text{OH})$ as intermediate stages ($\text{X} = \text{Cl}$ or NO_3). Zinc sulphate on dilution gives $\text{Zn}_3\text{SO}_4(\text{OH})_2$ and $[\text{Zn}(\text{OH})(\text{SO}_4)_2]^{3-}$. Hydrolysis of zinc chloride and

⁹⁶ I. Greenwald, *J. Biol. Chem.*, 1945, **161**, 697.

⁹⁸ (Mlle.) M. Gerbault, *Compt. rend.*, 1946, **223**, 732.

⁹⁹ J. R. Goldsmith, *J. Geol.*, 1948, **56**, 80.

¹ V. Cirilli, *Ric. Sci.*, 1947, **17**, 439; J. Brocard, *Compt. rend.*, 1946, **223**, 900.

² M. Erchak, junr., I. Fankuch, and R. Ward, *J. Amer. Chem. Soc.*, 1946, **68**, 2085, 2093.

³ H. F. Kay and R. G. Rhodes, *Nature*, 1947, **160**, 126.

⁴ (Miss) H. D. Megaw, *Trans. Faraday Soc.*, 1946, **A**, **42**, 225; *Proc. Physical Soc.*, 1946, **58**, 133; D. F. Rushman and M. A. Strivens, *Trans. Faraday Soc.*, 1946, **A**, **42**, 231; M. G. Harwood, P. Popper, and D. F. Rushman, *Nature*, 1947, **160**, 58; J. K. Hulm, *ibid.*, p. 127.

⁵ A. Ferrari and L. Cavalea, *Gazzetta*, 1946, **76**, 120.

⁷ L. Hackspill and (Mlle.) M. L. Jungfleisch, *Compt. rend.*, 1946, **223**, 181; (Mlle.) M. L. Jungfleisch, *ibid.*, p. 1003.

⁸ M. Pourbaix, *Bull. Soc. chim. Belg.*, 1944, **53**, 159.

⁹ E. Carrière, H. Guiter, and M. Anouar, *Bull. Soc. chim.*, 1946, **13**, 405; 1947, **14**, 72.

zinc sulphate by sodium hydroxide, however, yields no evidence¹⁰ of the formation of basic salts of definite composition; equilibrium is only reached some 48 hours after addition of reagent. Zinc acetates and acetato-chlorides have been studied.¹¹ D. B. Cruickshank¹² has described some new zinc ferro- and ferri-cyanide complexes where, in solutions containing Zn^{++} , $\text{K}_3\text{Fe}(\text{CN})_6$, and KI at concentrations of 0.001—0.0001N, the zinc acts preferentially as a link between ferro- and ferri-cyanide radicals. Singly-linked chains stable up to three units, doubly-linked up to five, appear to be formed along with branched chains, the maximum size of any type of chain being about eight units.

The conditions for the precipitation of cadmium hydroxide have been studied,¹³ and further papers¹⁴ have appeared on the basic cadmium sulphates. The thermal dissociation of cadmium iodide has been followed¹⁵ between 900° and 1200° by measurement of its absorption spectrum: the following equilibria exist, $\text{CdI} \rightleftharpoons \text{Cd} + \text{I}_2$, $\text{CdI}_2 \rightleftharpoons \text{CdI} + \text{I}$, and $\text{I}_2 \rightleftharpoons \text{I} + \text{I}$. Accurate measurements for the corresponding bromide were prevented by the overlapping of the spectra of bromine and salt vapour.

A detailed description¹⁶ has been given of a ten-cell countercurrent reflux still used for concentrating mercury isotopes. Mercury(II) sulphide has been investigated by W. D. Treadwell and F. Schaufelberger,¹⁷ who found the heat of formation to be -14 and -12.8 kcal. for cinnabar and metacinnabar respectively. The thermodynamic solubility product calculated for the black sulphide is much less than the experimental value: to account for this it is assumed that the acid $\text{H}_2[\text{HgS}_2]$ is formed. The hydrolysis of mercury(II) chloride and bromide both on aqueous dilution¹⁸ and on addition of sodium or potassium hydrogen carbonate or sodium pyrophosphate¹⁹ has been studied. L. G. Sillen and G. Ingel'dt²⁰ have reinvestigated the equilibria $\text{Hg}^{++} + \text{HgX}_2 \longrightarrow 2\text{HgX}^+$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$), have detected complexes and ion pairs involved in mercury(I) and mercury(II) nitrates and sulphates, and have measured their equilibrium constants. Red mercury(II) chlorite, soluble in dilute acids, has been prepared²¹ from carbonate-free sodium chlorite and mercury(II) nitrate (but

¹⁰ S. de Mende, *Compt. rend.*, 1948, **226**, 916.

¹¹ (Mlle.) M. Gerbault, *ibid.*, 1946, **222**, 1109.

¹² *Research*, 1948, **1**, 663.

¹³ (Mlle.) M. Quintin, *Compt. rend.*, 1948, **226**, 910.

¹⁴ *Ann. Reports*, 1944, **41**, 95; W. Feitknecht, *Helv. Chim. Acta*, 1945, **28**, 1444; W. Feitknecht and W. Gelber, *ibid.*, p. 1454; B. C. Halder, *J. Indian Chem. Soc.*, 1946, **23**, 147.

¹⁵ K. Wieland and A. Herczog, *Helv. Chim. Acta*, 1946, **29**, 1702.

¹⁶ A. K. Brewer and S. L. Madorsky, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 129.

¹⁷ *Helv. Chim. Acta*, 1946, **29**, 1936.

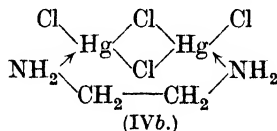
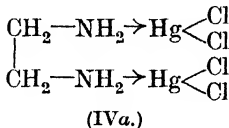
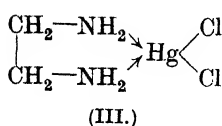
¹⁸ E. Carrière and M. Lafitte, *Bull. Soc. chim.*, 1945, **12**, 833; E. Carrière, H. Guiter, and M. Lafitte, *ibid.*, 1948, **15**, 23, 25.

¹⁹ J. Lamure, *Compt. rend.*, 1946, **222**, 1392.

²⁰ *Svensk Kem. Tidskr.*, 1946, **58**, 52, 61, 104.

²¹ O. Erämetsä, *Suomen Kem.*, 1942, **15**, B, 11.

not chloride), and various complex decomposition products of the chlorite have been described. T. D. O'Brien's work²² on some ethylenediamino-mercury(II) complexes has demonstrated the existence of Hg en Cl_2 (III), $\text{en}(\text{HgCl}_2)_2$ (IVa or IVb), $\text{Hg en}_2\text{SO}_4$ and $\text{Hg en}_2(\text{H}_2\text{O})_2\text{SO}_4$ ($\text{en} = \text{NH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$). The compound (IV) is soluble in excess of ethylene-



diamine reagent to form a complex which, from a break in the curve of refractive index against the ratio $\text{en} : \text{HgCl}_2$ at a value of 3 : 1 for that ratio, appears to be $(\text{Hg en}_3)\text{Cl}_2$. Evidence is thus given for 6-co-ordinated mercury(II) in that complex and presumably in $\text{Hg en}_2(\text{H}_2\text{O})_2\text{SO}_4$. The preparation of ethylmercury phosphates $(\text{HgEt})_2\text{HPO}_4$, $(\text{HgEt})\text{H}_2\text{PO}_4$, and $(\text{HgEt})_3\text{PO}_4$ has been described.²³

Group III.—Since the determination, by H. V. A. Briscoe and P. L. Robinson,²⁴ of the atomic weight of boron, a mass-spectrographic determination²⁵ of relative isotopic abundance has been needed to confirm the small differences in the ratio $^{11}\text{B} : ^{10}\text{B}$ which then seemed probable in samples from the various localities, *e.g.*, California, Tuscany, and Asia Minor. Such confirmation has now been obtained, and variations in the ratio range from 4.416 ± 0.004 (Tuscany) to 4.222 ± 0.004 (Stassfurt). In two cases the earlier chemical atomic weights compare very favourably with the mass spectrographic results :

| Source. | Mass-spectro-graphic. | Gravimetric. |
|-----------------|--------------------------|--------------|
| Tuscany | 10.826 | 10.825 |
| Turkey | 10.822 | 10.818 |
| California..... | { 10.822 } { 10.824 } | 10.840 |

Possible variation in isotopic abundance over the various parts of the California deposit has yet to be investigated, but better agreement with the gravimetric value does not seem likely.

Hydroborons have received extensive comment²⁶ recently and, for the present, only the important X-ray determination²⁷ of the structure of $\text{B}_{10}\text{H}_{14}$ need be remarked. With reference to related compounds, E. Wiberg has reviewed²⁸ wartime German work not only on the hydroborons, but

²² *J. Amer. Chem. Soc.*, 1948, **70**, 2771.

²³ A. D. Ainley, L. A. Elson, and W. A. Sexton, *J.*, 1946, 776.

²⁴ *J.*, 1925, 696; 1927, 282.

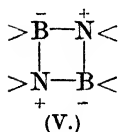
²⁵ H. G. Thode, J. Macnamara, F. P. Lessing, and C. B. Collins, *J. Amer. Chem. Soc.*, 1948, **70**, 3008.

²⁶ *Ann. Reports*, 1947, **44**, 52; *Quart. Reviews*, 1948, **2**, 132.

²⁷ J. S. Kasper, C. M. Lucht, and D. Harker, *J. Amer. Chem. Soc.*, 1948, **70**, 881; G. Silbiger and S. H. Bauer, *ibid.*, p. 115.

²⁸ *Ref. 5*, p. 126.

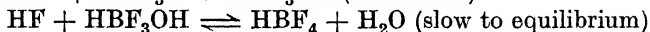
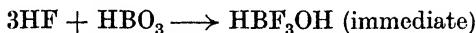
also on the range of compounds $\text{BH}_3\cdot\text{NH}_3$, $\text{BH}_2\cdot\text{NH}_2$, $\text{BH}\cdot\text{NH}$ and on a wide variety of derivatives with substituents F, Cl, Br, Me, Et, OH, NMe_2 , NHMe, Ph. The tendency of borazene ($\text{BH}_2\cdot\text{NH}_2$) derivatives to dimerise, and of borazine ($\text{BH}\cdot\text{NH}$) to trimerise to borazole derivatives, is shown ²⁹ to depend on the extent to which substituents



influence the resonance between $\bar{\text{B}}=\overset{+}{\text{N}}\text{--}$ and $\text{--}\bar{\text{B}}-\overset{+}{\text{N}}\text{--}$.

Dimerisation to (V) will be favoured by a larger contribution of the former canonical, and thus by substituents at the boron atom in the order $\text{Cl} > \text{Br} > \text{H} > \text{CH}_3 > \text{C}_2\text{H}_5 > \text{NR}_2$, and in the reverse order at the nitrogen atom.

Borazole and derivatives ³⁰ and boron nitride ³¹ are also considered by Wiberg. There is some overlap with J. Goubeau's account, ³² in the same volume, of German work on boron halides, boron oxide, methyl esters of boric acid, and trimethyl- and triethyl-boron and derivatives. The thermodynamic stability of the ethylaminotrimethylborons ($\text{BMe}_3\cdot\text{NH}_n\text{Et}_{3-n}$) has been studied. ³³ Neither Wiberg and K. Hertwig ³⁴ nor A. W. Laubengayer and G. F. Condikey ³⁵ have found any evidence for any compound formation between BF_3 and NH_3 , other than $\text{BF}_3\cdot\text{NH}_3$. The latter authors have prepared this substance in quantity and find it to be monomeric and undissociated in aqueous solution, with a heat of formation from gaseous ammonia of 41.3 kcal./mole at 0°. At 125° the compound disproportionates thus, $4\text{NH}_3\cdot\text{BF}_3 \longrightarrow 3\text{NH}_4\text{BF}_4 + \text{BN}$, and vapour pressure values for heated $\text{NH}_3\cdot\text{BF}_3$ are in fact those for NH_4BF_4 , the only volatile decomposition product below 150°. C. A. Wamser ³⁶ has shown from conductivity measurements that the formation of tetrafluoroboric acid is stepwise, as follows :



He and I. G. Rys ³⁷ have prepared KBF_3OH which is shown to be identical with the previously reported $\text{K}_2\text{B}_2\text{F}_6\cdot 1.5\text{H}_2\text{O}$. D. R. Martin ³⁸ has reviewed the formation of co-ordination compounds of boron halides and shown that the boron atom weakens as an electron acceptor from BF_3 to BI_3 .

Aluminium phosphide has been prepared ³⁹ as a black solid which dissociates before melting. Mixed aqueous solutions of aluminium fluoride and sulphate give, ⁴⁰ on treatment with ammonia, compounds in the range

²⁹ E. Wiberg, A. Bolz, P. Buchheit, and K. Hertwig, *J. Amer. Chem. Soc.*, 1948, **70**, 133.

³⁰ *Ibid.*, p. 138.

³¹ E. Wiberg and A. Bolz, *Ber.*, 1940, **73**, 209.

³² Ref. 5, p. 226.

³³ H. C. Brown and M. D. Taylor, *J. Amer. Chem. Soc.*, 1947, **69**, 1332.

³⁴ Ref. 5, p. 217.

³⁵ *J. Amer. Chem. Soc.*, 1948, **70**, 2274.

³⁶ *Ibid.*, p. 1209.

³⁷ *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **54**, 325.

³⁸ *J. Physical Coll. Chem.*, 1947, **51**, 1400; *Chem. Reviews*, 1948, **42**, 581.

³⁹ E. Montignie, *Bull. Soc. chim.*, 1946, **13**, 276.

⁴⁰ J. M. Cowley and T. R. Scott, *J. Amer. Chem. Soc.*, 1948, **70**, 105.

$\text{AlF}(\text{OH})_2$ to $\text{AlF}_2(\text{OH})$. X-Ray study shows that these, on heating, decompose directly into AlF_3 and $\text{Al}(\text{OH})_3$, with no evidence for AlOF . Raman spectra of molten $\text{AlCl}_3 \cdot \text{NH}_3$ indicate¹¹ that the additive compound involves AlCl_3 and not Al_2Cl_6 . The hydrolysis of aluminium chloride has been found⁴² to yield first $\text{H}_3[\text{AlCl}_3(\text{OH})_3]$ and then at greater dilution $\text{H}_3[\text{AlCl}_2(\text{OH})_4]$; the sulphate gives $\text{H}[\text{Al}(\text{SO}_4)(\text{OH})_2]$. There is evidence⁴³ that the precipitation of alumina from sodium aluminate solutions by carbon dioxide at 60° proceeds according to $2\text{AlO}_2^- + 2\text{H}_3\text{O}^+ \longrightarrow \text{Al}_2\text{O}_3 \cdot 2\text{H}_2\text{O}$.

There appears to be nothing to add to the reported⁴⁴ chemistry of gallium, but the chemistry of indium has received attention in a series of papers by T. Moeller concerned with the hydrolysis of indium halide⁴⁵ and the precipitation of the hydroxide,⁴⁶ an organic precipitant for indium,⁴⁷ and the formation of indates⁴⁸ and oxalato-indates.⁴⁹ F. Ensslin and S. Valentiner⁵⁰ have also prepared a number of indates by fusion of $\text{In}(\text{NO}_3)_3$ with various metal nitrates. Ensslin and O. Lessmann⁵¹ have plotted the system In_2O_3 - SO_3 - H_2O at 20° , 40° , and 60° and have measured the solubility of indium trihalides in non-aqueous solvents.

Thallium sulphate treated with ammonium hydroxide and hydrogen sulphide at 50° under nitrogen gives⁵² thallium sulphide. On admitting oxygen, a moderate reaction occurs, catalysed by water vapour, and black Tl_2S gives way to olive-brown $\alpha\text{-Tl}_2\text{SO}_2$. Though this compound is stable in air at room temperature it changes slowly into greenish-yellow $\beta\text{-Tl}_2\text{SO}_2$ when heated in a vacuum to 250° . Chemically, both forms are thallium(I) sulphyxylate, though X-ray study shows them to be of different structure, the first of which has not been previously reported: both forms differ from Tl_2S . Though thallium has hitherto been regarded as having little tendency to form with organic acids normal and inner complexes insoluble in water, F. Feigl⁵³ has prepared stable inner complex salts of thallium(III) with such agents as nitrosonaphthylhydroxylamine and 8-hydroxyquinoline. Thallium(I) ferrate(III), TlFeO_2 , has been described.⁵⁴

Group IV.—Bands have been observed⁵⁵ in the spectra of comets attributable to the molecules $^{12}\text{C}^{13}\text{C}$ and $^{13}\text{C}^{13}\text{C}$. The relative abundance of ^{13}C

⁴¹ J. Goubeau and H. Siebert, *Z. anorg. Chem.*, 1947, **254**, 126.

⁴² E. Carrière and P. Faure, *Bull. Soc. chim.*, 1942, **9**, 809; M. Le Peintre, *Compt. rend.*, 1946, **223**, 1004.

⁴³ K. L. Elmore, C. M. Mason, and J. D. Hatfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1449.

⁴⁴ *Ann. Reports*, 1944, **41**, 102.

⁴⁵ *J. Amer. Chem. Soc.*, 1940, **62**, 1206; 1942, **64**, 953, 2234.

⁴⁶ *Ibid.*, 1941, **63**, 2625.

⁴⁷ *Ind. Eng. Chem. Anal.*, 1943, **15**, 270.

⁴⁸ T. Moeller and J. G. Schnizlein, *J. Physical Coll. Chem.*, 1947, **51**, 771.

⁴⁹ *J. Amer. Chem. Soc.*, 1940, **62**, 2444.

⁵⁰ *Z. Naturforsch.*, 1947, **2b**, 5.

⁵¹ *Z. anorg. Chem.*, 1947, **254**, 83, 92.

⁵² J. Fentress and P. W. Selwood, *J. Amer. Chem. Soc.*, 1948, **70**, 711.

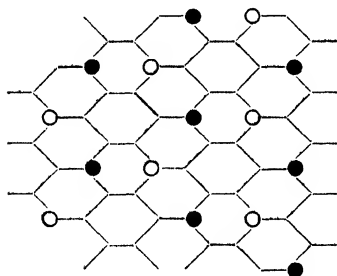
⁵³ *Nature*, 1948, **161**, 436.

⁵⁴ K. Kapitancyk, *Rocz. Chem.*, 1946, **20**, 33.

⁵⁵ J. Dufay, *Compt. rend.*, 1946, **228**, 783.

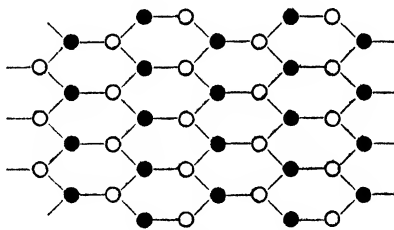
in comets is more than 1%. Chemical compounds⁵⁶ in which ^{14}C appears [produced by an (n,p) reaction from ^{14}N], and the uses of the isotope as a tracer, are surveyed.⁵⁷ A symposium⁵⁸ on diamond reviews crystal form, structure, and associated physical phenomena, and D. P. Mellor⁵⁹ has discussed the synthesis of diamond. The action of hydrogen atoms (20% at 0.4 mm. Hg) on soot deposits at 45° yields⁶⁰ mainly methane with small amounts of hydrocarbons $\text{C}_2\text{—C}_5$ and no products involatile at -100° . In agreement with current ideas on combustion, J. R. Arthur⁶¹ has found that when carbon is burning in air the gas within a fraction of a mm. of the surface contains 0.5—2.5% of carbon monoxide, but away from it the carbon monoxide content is negligible. With inhibitors present, up to 22% of carbon monoxide was found in gas taken from about 1 mm. from the surface. The monoxide is produced heterogeneously and oxidised homogeneously by a chain mechanism sensitive to chlorine. W. Rüdorff⁶² reviews work on the interesting interstitial compounds graphite oxide and graphitic salts (nitrate, perchlorate, and, *e.g.*, $[\text{C}_{24}]^+\text{HF}_2^-, 2\text{H}_2\text{F}_2$ or $[\text{C}_{24}]^+\text{HSO}_4^-, 2\text{H}_2\text{SO}_4$).

A new carbon fluoride, $(\text{C}_4\text{F})_n$, has been described⁶³ and has graphite structure with the fluorine atoms located alternately above and below the graphite sheets as shown (VI) with C-F distance 1.4 Å. Carbon mono-



(VI.)

(F atom ○ above and ● below the graphite sheet.)



(VII.)

fluoride, $(\text{CF})_n$, has similar structure (VII) though the graphite planes are probably puckered, and distances have been reported as

| | |
|------------------------|--|
| C-C (interlayer) | 6.75, ⁶⁴ 6.0 ⁶⁵ Å. |
| C-C (ring) | 1.54, 1.49 Å. |

⁵⁶ L. D. Norris and A. H. Snell, *Science*, 1947, **105**, 265; P. E. Yankwich, G. K. Rollefson, and T. H. Norris, *J. Chem. Physics*, 1946, **14**, 131; R. B. Loftfield, *Nucleonics*, 1947, **1**, 54.

⁵⁷ W. W. Miller and T. D. Price, *ibid.*, p. 11.

⁵⁸ *Proc. Indian Acad. Sci.*, 1946, **A**, **24**, 1.

⁵⁹ *J. Chem. Physics*, 1947, **15**, 525.

⁶⁰ G. M. Harris and A. W. Tickner, *Nature*, 1947, **160**, 871.

⁶¹ *Ibid.*, 1946, **157**, 732.

⁶² Ref. 5, p. 244.

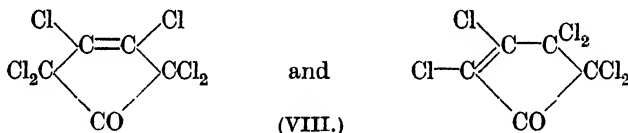
⁶³ W. Rüdorff and G. Rüdorff, *Ber.*, 1947, **80**, 417.

⁶⁴ *Idem*, *ibid.*, p. 413.

⁶⁵ D. E. Palin and K. D. Wadsworth, *Nature*, 1948, **162**, 925.

the second values being from a sample whose density suggests an interlayer distance of 6.3 Å. An unexpectedly large value of 231 ± 3 kcal./mole has been obtained⁶⁶ for the heat of formation of CF_4 , and 142 ± 1 is the value obtained for COF_2 . A method has been described⁶⁷ of preparing carbon monoxide (designed for ^{13}CO) by heating dry calcium carbonate and twice the theoretical amount of zinc to 750° —the product contains 99.1% of carbon monoxide.

The properties of COSe , COTe , $\text{CO}(\text{CN})_2$, $\text{H}\cdot\text{COF}$, COClF , COBrF , COIF , COF_2 have been reviewed by W. Rüdorff.⁶⁸ Carbonyl chlorofluoride COFCl , has been prepared⁶⁹ by shaking hydrogen fluoride and carbonyl chloride in a copper bomb at 80° and 280 lb./sq. in. The product, after separation from carbonyl fluoride simultaneously produced, had b. p. -42° , m. p. -138° , mol. wt. 82.5; it is readily absorbed by sodium hydroxide, but does not react with glass. Raman spectra have shown⁷⁰ that the compound C_6Cl_6 has a cyclic structure (hexachlorocyclopentadiene) and that $\text{C}_6\text{Cl}_6\text{O}$ has two isomers (VIII).



The chemistries of carbon and silicon have been contrasted and compared.⁷¹ The thermal decomposition of di- and tri-silane has been the subject of kinetic study⁷² which discredits the importance previously ascribed to silyl radicals in the decomposition, and H. J. Emeléus and A. G. Maddock⁷³ have described the preparation and properties of tetrasilane. Two reports of interest concern the preparation of synthetic quartz. In the first, fused silica is described⁷⁴ as being mainly converted into quartz when heated, at a suitable temperature, in a solution of sodium silicate. Some of the crystals were perfect though small. A natural quartz crystal showed appreciable overgrowth in a few hours when suspended near a rod of fused silica in a bath containing a "mineraliser". In the second,⁷⁵ quartz was synthesised by heating silicic acid in an autoclave with potassium or sodium carbonate solution for three days at 350 – 390° . The vapour of caesium fluoride proves⁷⁶ to be a mineraliser bringing about the rapid transformation of vitreous silica into cristobalite at 800° .

⁶⁶ H. von Wartenberg, *Nach. Ges. Wiss. Göttingen*, 1946, 55, 57.

⁶⁷ S. Weinhouse, *J. Amer. Chem. Soc.*, 1948, 70, 442.

⁶⁸ O. Glemser, T. Risler, V. Hänsser, and H. Sauer, ref. 5, p. 239.

⁶⁹ J. H. Simons, D. F. Herman, and W. H. Pearson, *J. Amer. Chem. Soc.*, 1946, 68, 1672.

⁷⁰ H. Gerding, H. J. Prius, and H. V. Brederode, *Rec. Trav. chim.*, 1946, 65, 168, 174.

⁷¹ R. Schwarz, *Chemie*, 1943, 56, 258.

⁷² K. Stokland, *Trans. Faraday Soc.*, 1948, 44, 545. ⁷³ *J.*, 1946, 1131.

⁷⁴ N. Wooster and W. A. Wooster, *Nature*, 1946, 157, 297.

⁷⁵ R. M. Barrer, *ibid.*, p. 734; see also G. Van Praagh, *Geol. Mag.*, 1947, 84, 98.

⁷⁶ R. Caillat, *Ann. Chim.*, 1945, 20, 367.

Silicon tetrafluoride has been shown ⁷⁶ to have no action on N_2O_5 , N_2O_4 , or 99% HNO_3 , but to be absorbed with hydrolysis in ordinary concentrated nitric acid and by 62.5% sulphuric acid. It is quantitatively hydrolysed by water, $3\text{SiF}_4 + 3\text{H}_2\text{O} \longrightarrow 2\text{H}_2\text{SiF}_6 + \text{H}_2\text{SiO}_3$, the resulting solution containing no free hydrogen fluoride. All three fluoroisocyanates of silicon have been prepared; ⁷⁷ the synthesis ⁷⁸ and partial hydrolysis ⁷⁹ of silicon tetrachloride and the formation of plastic chlorides, ⁸⁰ e.g., $\text{Si}_{25}\text{Cl}_{52}$, have been described. The latter are obtained by pyrolysis of the tetrachloride in nitrogen at 1250° : on hydrolysis they yield $\text{Si}_6(\text{OH})_{10}\text{O}_2$ which has been formulated $\text{SiO}(\text{OH})\cdot[\text{Si}(\text{OH})_2]_4\cdot\text{SiO}\cdot\text{OH}$. H. H. Sisler and J. C. Cory ⁸¹ have obtained molecular addition compounds between diphenyl ether or anisole and chlorides of silicon, germanium, and tin: the compounds are described and none was observed with carbon tetrachloride.

Since the full report ⁸² on the chemistry of germanium given in 1944, the reaction between GeMg_2 and ammonium bromide has been shown ⁸³ to yield three germanium hydrides, GeH_4 , Ge_2H_6 , and Ge_3H_8 , for which thermal properties are given. The first, obtained in 30% yield, has m. p. -166° and b. p. -88° . Dibasic monogermanic acid has been assigned ⁸⁴ the formula H_4GeO_4 on the basis of a comparison with H_2CO_3 , H_2SO_3 , etc. Possible structures for pentagermanic acid have been considered and evidence for the equilibrium $5\text{H}_4\text{GeO}_4 \rightleftharpoons \text{H}_2\text{Ge}_5\text{O}_{11} + 9\text{H}_2\text{O}$. Treatment of dimethylgermanium dichloride, $(\text{CH}_3)_2\text{GeCl}_2$, with hydrogen sulphide leads ⁸⁵ to a white waxy solid, $(\text{CH}_3)_2\text{GeS}$, soluble, unlike GeS_2 , in acetone. Hydrolysis of the compound yields $(\text{CH}_3)_2\text{GeO}$ in crystalline, probably tetrameric, form. Atomic hydrogen reduces ⁸⁶ stannous chloride to tin, stannane, and hydrogen chloride. The production of stannane is said to be increased by the presence of methane, but in these circumstances the formation of metallic methyls must not be overlooked.

H. Jeffreys ⁸⁷ has considered the evidence given for the age of the earth by the relative abundance of the lead isotopes—one estimate ⁸⁸ of the age of terrestrial uranium is $(2.9 \pm 0.3) \times 10^9$ years. An interesting addition to our knowledge of the colouring of litharge is the observation ⁸⁹ that only tetragonal PbO is oxidised to red lead, Pb_3O_4 , when heated in

⁷⁷ G. S. Forbes and H. H. Anderson, *J. Amer. Chem. Soc.*, 1947, **69**, 1241.

⁷⁸ J. J. Dodonov and M. N. Tschurmanteeva, *J. Gen. Chem. Russia*, 1946, **16**, 1949.

⁷⁹ W. C. Schumb and A. J. Stevens, *J. Amer. Chem. Soc.*, 1947, **69**, 726.

⁸⁰ R. Schwarz and C. Danders, *Ber.*, 1947, **80**, 444.

⁸¹ H. H. Sisler and J. C. Cory, *J. Amer. Chem. Soc.*, 1947, **69**, 1515.

⁸² *Ann. Reports*, 1944, **41**, 108.

⁸³ K. Clusius and G. Farber, *Z. physikal. Chem.*, 1942, **B**, **51**, 352.

⁸⁴ G. Carpeni, *J. Chim. physique*, 1948, **45**, 128; A. Tchakirian and G. Carpeni, *Compt. rend.*, 1948, **226**, 1094.

⁸⁵ E. G. Rochow, *J. Amer. Chem. Soc.*, 1948, **70**, 1801.

⁸⁶ V. M. Vdovenko, *J. Gen. Chem. Russia*, 1945, **15**, 581.

⁸⁷ *Nature*, 1948, **162**, 822.

⁸⁸ F. G. Houtermans, *Z. Naturforsch.*, 1947, **2a**, 322.

⁸⁹ A. V. Pamfilov, E. G. Ivancheva, and A. G. Ivancheva, *J. Gen. Chem. Russia*, 1946, **16**, 325.

air, and that the rhombic variety must first be converted into the tetragonal form for reaction to take place. As might be expected, grinding, by deforming the lattice, enhances oxidisability. A reversible reaction⁹⁰ between lead and sulphur dioxide probably follows the course. $5\text{Pb} + 3\text{SO}_2 \rightleftharpoons \text{PbSO}_4 \cdot 2\text{PbO} + 2\text{PbS}$. Evidence has been given⁹¹ for the existence of the ion $[\text{Pb} \cdot \text{OAc}]^+$ over a wide range of concentration in aqueous solution of lead nitrate and ammonium acetate, and E. Grillot⁹² has prepared some solid acetato-lead halides. Lead pentafluoroaluminate(-2), PbAlF_5 , has been described.⁹³ General surveys⁹⁴ have been made in the production (especially by calcium reduction⁹⁵ of the oxide), properties, and technical uses of zirconium and titanium. Pure ductile titanium has been prepared⁹⁶ by decomposing titanium iodide vapour on a hot filament. Reductions of titanium dioxide by heating with calcium, magnesium, and hydrogen yield⁹⁷ a variety of oxides: Ti_3O_5 , Ti_3O_4 , Ti_2O_3 , TiO . With hydrogen,⁹⁸ Ti_3O_5 is produced at 900° , though in the presence of calcium chloride reduction commences at 320° to yield an unidentified blue product.

Zirconium hydride and metal have been obtained⁹⁹ by reducing the oxide with 10% excess of magnesium chips at 900° in hydrogen. The excess of magnesium is distilled off in the presence of hydrogen, leaving ZrH_4 , which, heated in a vacuum, gives the metal. Neat methods¹ of obtaining the metal from difficultly reducible oxides, such as those of zirconium and the lanthanons, are: (i) placing the oxide on a concave tungsten disc which forms the cathode of a hydrogen arc struck at 300—400 mm. pressure, (ii) blowing the powdered oxide through a graphite tube in which a hydrogen arc, maintained between the wall of the tube and an axial graphite cathode, is caused to rotate by means of an axial magnetic field. The fractional separation of hafnium and zirconium by means of triethyl phosphate appears promising:² the hafnium content, in weight %, is increased from 16 to 91 in five steps, 16% of the original hafnium being recovered in the concentrate. Hafnium and zirconium may be separated³ completely from aluminium by a method depending upon the fact that within the concentration range 30—40% HCl the solubility of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ decreases greatly whereas that of ZrOCl_2 or HfOCl_2 increases greatly with

⁹⁰ A. Chrétien and J. Broglin, *Compt. rend.*, 1947, **225**, 1315.

⁹¹ B. C. Purkayastha and R. N. Sen-Sarma, *J. Indian Chem. Soc.*, 1946, **23**, 31.

⁹² *Compt. rend.*, 1946, **223**, 151; *Bull. Soc. chim.*, 1948, **15**, 284.

⁹³ T. R. Scott, *J. Coun. Sci. Ind. Res. Australia*, 1947, **20**, 114.

⁹⁴ W. J. Kroll and A. W. Schlechten, *Metal Ind.*, 1946, 69; W. H. Waggaman and E. A. Gee, *Chem. Eng. News*, 1948, **26**, 377.

⁹⁵ W. C. Lillendahl and H. C. Rentschler, *Trans. Electrochem. Soc.*, 1947, **91**, Preprint, p. 237.

⁹⁶ I. E. Campbell, R. I. Jaffee, J. M. Blocker, junr., J. Gurland, and B. W. Gonsler, *J. Electrochem. Soc.*, 1948, **93**, 271.

⁹⁷ A. Chrétien and R. Wyss, *Compt. rend.*, 1947, **224**, 1642.

⁹⁸ R. Wyss, *Ann. Chim.*, 1948, **3**, 215.

⁹⁹ L. W. Davis, U.S.P. 2,411,524.

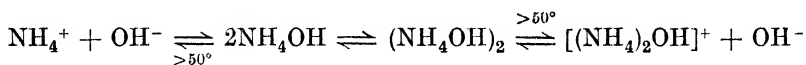
¹ D. L. Simonenko, *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **51**, 303.

² H. H. Willard and H. Freund, *Ind. Eng. Chem. Anal.*, 1946, **18**, 195.

³ W. Fischer and M. Zumbusch, *Z. anorg. Chem.*, 1944, **252**, 249.

rising acid concentration. If aluminium is in excess, it is precipitated by saturation with hydrogen chloride and zirconium is recovered from the filtrate: on the other hand, if zirconium is in excess, most of it is removed by a preliminary crystallisation from 25% HCl. Alternation of these processes give a quantitative separation. After preheating to 1450—1950°, 96—99% pure specimens of ZrO_2 show ⁴ rapid and large change in length in heating and cooling between room temperature and 1700°: a monoclinic-tetragonal transformation is the probable cause. A black, water-insoluble zirconium telluride, Zr_2Te , has been described.⁶

Group V.—The violence of the thermal dissociation of ammonium dichromate is reduced ⁷ by the addition of 2 parts of coarsely crushed ammonium sulphate; the reaction being thus rendered a convenient method for the preparation of nitrogen. K. Stewart ⁸ has investigated the action of active nitrogen on hydrazoic acid where the ultimate products are hydrogen, nitrogen, and, if hydrogen is present initially, ammonia. The results are interpreted in terms of the intermediate imine radical, NH . Thermal, electrical, and magnetic properties ⁹ and the photoconductivity ¹⁰ of solutions of metals in liquid ammonia have been measured. The considerable stability of these highly conducting metallic-character solutions is thought to lie in the high activation energy of the electron addition $\epsilon + \text{NH}_3 \longrightarrow \text{NH}_2^- + \text{H}$ in liquid ammonia. The oxidation by dry air of ammonia, adsorbed on coconut charcoal, is found ¹¹ to give hydroxylamine in 8 hours and ammonium nitrite in several days. Ammonium salts in aqueous solution give ¹² nitrite and nitrate ions on exposure to ultra-violet radiation. Though data on the precipitation of magnesium hydroxide by ammonia have been interpreted ¹³ on the basis of the equilibria



P. F. van Velden and J. A. A. Ketelaar,¹⁴ in a critical review of theoretical and experimental work in all phases, conclude that there is no evidence for the existence of ammonium hydroxide. The reactions between ammonia and the oxides of nitrogen have been investigated,¹⁵ and the dissociation pressure of ammonium carbamate measured.¹⁶

⁴ R. F. Geller and P. J. Yavorsky, *J. Res. Nat. Bur. Stand.*, 1945, **35**, 87.

⁶ E. Montignie, *Ann. Pharm. Franç.*, 1946, **4**, 253.

⁷ R. C. L. Bosworth, *J. Proc. Roy. Soc. New South Wales*, 1946, **79**, 116.

⁸ K. Stewart, *Trans. Faraday Soc.*, 1945, **41**, 663.

⁹ A. J. Birch and D. K. C. McDonald, *ibid.*, 1948, **44**, 735.

¹⁰ R. A. Ogg, junr., *J. Chem. Physics*, 1946, **14**, 399.

¹¹ C. Courty and L. Rougeot, *Compt. rend.*, 1946, **223**, 624.

¹² R. Cultrera, *Gazzetta*, 1946, **76**, 187.

¹³ (Mlle.) G. Gallin, *Ann. Chim.*, 1946, **1**, 277.

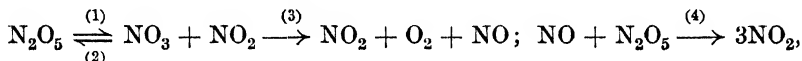
¹⁴ *Chem. Weekblad*, 1947, **43**, 401.

¹⁵ M. Patry, R. Garlet, and S. Pupko, *Compt. rend.*, 1947, **225**, 941.

¹⁶ E. P. Egan, junr., J. E. Potts, junr., and G. D. Potts, *Ind. Eng. Chem.*, 1946,

The production of dinitrogen oxide, N_2O , by thermal decomposition of ammonium nitrate has been followed¹⁷ with ^{15}N as a tracer, the ammonium containing 62% of ^{15}N and the nitrate 0.38%. The expected amounts of $^{15}N_2O$ in the product were 9.6% for random combination of all nitrogen atoms, and 0.24% for reaction entirely between one atom from the ammonium group and one from the nitrate group. The found value of 0.35% suggests the latter mechanism ${}^aNH_4{}^bNO_2 \longrightarrow {}^aN^bNO + 2H_2O$ with little or no aN_2O or bN_2O . Dinitrogen oxide has been identified¹⁸ in the atmosphere and appears to be present to the same extent over England and America.

The preparation and properties of sodium hyponitrite ($Na_2N_2O_2 \cdot 5H_2O$) have been described,¹⁹ and Na, K, Ca, Ba, Sr, Cd, and Pb salts of hyponitric acid, $H_2N_2O_3$, have been prepared;²⁰ the dry salts are stable in dry air and stable to carbon dioxide; the alkali-metal salts are unstable in water and the others insoluble. The action of acids, and of heat, give nitrogen monoxide as the main product. R. A. Ogg, junr.,²¹ has measured the heat of solution of dinitrogen pentoxide in water, and from it he deduces that in a decomposition mechanism,



reaction (3) will be slow compared with reaction (2), and reaction (4) will be rapid. The overall rate constant, apparently first order, will thus be a product of an equilibrium constant and a second-order rate constant.

Work on peroxyntic acid has been reviewed²²—the action of hydrogen peroxide on nitryl chloride, NO_2Cl , and on dinitrogen pentoxide yields HNO_4 in only the second case. The first leads to the formation of nitrous and hypochlorous acids, from which M. Schmeisser and R. Schwarz²³ conclude that nitryl chloride is (IX) and not (X), and that no true chloride



of nitric acid exists. A review of nitrosyl compounds has been made,²⁴ and a tentative classification advanced based on nitrogen as an electron donor. A new mode of formation of nitrosyl compounds has been described,²⁵ using hydroxylamine, which appears to give the required NO group by a disproportionation mechanism.

Nitrogen trifluoride and NHF_2 , but not NH_2F , are among the products²⁶

¹⁷ J. T. Kummer, *J. Amer. Chem. Soc.*, 1947, **69**, 2559.

¹⁸ J. H. Shaw, G. B. B. M. Sutherland, and T. W. Wormell, *Physical Rev.*, 1948, **74**, 978.

¹⁹ T. M. Oza, *J. Indian Chem. Soc.*, 1945, **22**, 225.

²⁰ K. G. Naik, C. C. Shah, and S. Z. Patel, *ibid.*, 1946, **23**, 284, 341.

²¹ *J. Chem. Physics*, 1947, **15**, 337.

²² R. Schwarz and U. Gregor, ref. 5, p. 197.

²³ *Ibid.*, p. 199.

²⁴ T. Moeller, *J. Chem. Educ.*, 1946, **23**, 542.

²⁵ W. Heiber and R. Nast, *Z. Naturforsch.*, 1947, **2b**, 321.

²⁶ W. Kwaenik, ref. 5, p. 204.

of electrolysis of fused ammonium fluoride, the exact result depending upon the nature of the anode material—nickel or I.G. Werk Griesheim electrode carbon gives fluorine, Swedish graphite gives nitrogen, and American graphite NH_3 , NHF_2 , and N_2 . The melting point of nitrogen trichloride has been measured,²⁷ and its explosive properties investigated²⁸ as a function of pressure. Attempts to produce nitrogen tribromide by electric discharge in the elements were without success,²⁹ but in the presence of ammonia an intense red compound has been observed,³⁰ identical with that produced³¹ by the reaction between bromine cyanide and ammonia in ethyl chloride and which decomposes explosively at -67° to nitrogen, ammonium bromide, and ammonia in molecular proportions 1 : 3 : 2. The red compound has been assigned the formula $\text{NBr}_3 \cdot 6\text{NH}_3$ on the basis of this result, though attempts to obtain NBr_3 from it failed.³²

The conversion of colourless phosphorus into red—the term yellow persists for the colourless variety of the element and is to be found in an otherwise excellent text issued recently—has been studied³³ between 250° and 350° . It is a first-order reaction, without either autocatalysis or evidence of surface reaction on the particles of the red form, and occurring rather by the coalescence of nuclei into porous aggregates. The oxidations of red³⁴ and of colourless³⁵ phosphorus have been studied; F. S. Dainton³⁶ has pointed to the importance of bond energies X-X and X-O ($\text{X} = \text{P}, \text{As}, \text{Sb}$) in the oxidation of those elements. Hypophosphorous acid has been obtained³⁷ in high purity by oxidising phosphine with a suspension of iodine in water, $\text{PH}_3 + 2\text{I}_2 + 2\text{H}_2\text{O} \longrightarrow \text{H}_3\text{PO}_2 + 4\text{HI}$, and products of higher oxidation are not formed. A well-documented review³⁸ of the sodium phosphates is available. Thermal analysis³⁹ and infra-red spectra⁴⁰ of sodium phosphate melts indicate the existence of $(\text{NaPO}_3)_3$ and $(\text{NaPO}_3)_2$, and R. N. Bell⁴¹ has found all liquid phosphoric acids between $\text{H}_2\text{O} \cdot \text{P}_2\text{O}_5$ and $3\text{H}_2\text{O} \cdot \text{P}_2\text{O}_5$ to be mixtures of the four species H_3PO_4 , $\text{H}_4\text{P}_2\text{O}_7$, $\text{H}_5\text{P}_3\text{O}_{10}$, and $(\text{HPO}_3)_6$, and another, unidentified acid measured by difference. On

²⁷ M. Schmeisser, ref. 5, p. 173.

²⁸ A. J. Apin, *J. Physical Chem. Russia*, 1940, **14**, 494.

²⁹ P. W. Schenk and H. Jablonowski, *Z. anorg. Chem.*, 1940, **244**, 397.

³⁰ M. Schmeisser, *ibid.*, 1941, **246**, 284.

³¹ L. Birchenbach and M. Linhard, *ibid.*, 1941, **247**, 307.

³² M. Schmeisser, ref. 5, p. 174.

³³ T. W. DeWitt and S. Skolnik, *J. Amer. Chem. Soc.*, 1946, **68**, 2305; S. Skolnik, G. Tarbuton, and W. E. Bergman, *ibid.*, p. 2310.

³⁴ M. S. Silverstein, G. F. Nordblom, C. W. Ditttrich, and J. J. Jakabeim, *Ind. Eng. Chem.*, 1948, **40**, 301.

³⁵ F. S. Dainton and J. C. Bevington, *Trans. Faraday Soc.*, 1946, **42**, 377.

³⁶ *Ibid.*, 1947, **43**, 244.

³⁷ R. Paris and P. Tardy, *Compt. rend.*, 1946, **223**, 242.

³⁸ O. T. Quinby, *Chem. Reviews*, 1947, **40**, 141.

³⁹ (Mile.) D. Kantzer, *Compt. rend.*, 1947, **225**, 1317.

⁴⁰ J. Lecante, A. Boullé, and (Mme.) M. Dominé-Bergès, *Bull. Soc. chim.*, 1948, **15**, 764.

⁴¹ *Ind. Eng. Chem.*, 1948, **40**, 1464.

the other hand, in the hydration of pyrophosphoric acid V. N. Osipov⁴² has found evidence for $H_{10}P_4O_{15}$, of which magnesium and zinc salts (8 hydrogen atoms replaced) are described. Fluorophosphoric acid, H_2PO_3F , has been prepared⁴³ by the action of hydrogen fluoride on the pentoxide or the meta-acid at moderate temperatures. It is a colourless oily liquid, d_{25}^{25} 1.82, which does not attack glass and is a catalyst for polymerisation, condensation, alkylation, etc. Its esters are surface-active agents. (Mlle.) M. L. Delwaulle and F. François⁴⁴ have summarised the large number of measurements which they have recently made of the Raman spectra of compounds of the type PX_3 and $PX_3(O,S)$ (X = halogen), prepared by the methods of H. S. Booth and his collaborators.⁴⁵ The compounds measured are listed herewith :

| | | | | | | |
|---------|----------|----------|------------|------------|-----------|-----------|
| | PCl_3 | PBr_3 | PCl_3Br | $PClBr_2$ | | $PFClBr$ |
| POF_3 | $POCl_3$ | $POBr_3$ | $POCl_2Br$ | $POClBr_2$ | POF_2Cl | POF_2Br |
| | $PSCl_3$ | $PSBr_3$ | $PSCl_2Br$ | $PSClBr_2$ | $PSFCl_2$ | $PSFBr_2$ |
| | | | | | $PSFClBr$ | $PSFBrBr$ |

O. Schmitz-Dumont⁴⁶ has reviewed the German work on phosphorus nitrogen compounds. The trimer and the tetramer of $NPBr_2$ have been prepared,⁴⁷ and a number of phenyl derivatives of $P_4N_4Cl_4$.⁴⁸

The density of liquid arsine has been measured⁴⁹ between -60° and 30.5° . Solubility studies⁵⁰ on arsenic trioxide suggest the possibility of two fractions, a small one very soluble, and a bigger fraction only slightly soluble. Preparation of metallic antimony by high-temperature electrolysis has been described.⁵¹ A detailed physicochemical investigation⁵² has been made of antimonous acid, solutions of which were prepared by the action of hydrochloric acid on pure $Ag[Sb(OH)_6]$, itself obtained from silver nitrate and potassium antimonate. Molecular-weight determinations of arylstibonic acids show⁵³ that in the solid state high-molecular-weight polymers exist but that in solution $[ArSb(O_3H)]^-$ exists, changing to $[ArSb(OH)_5]^-$ in alkaline solution. F. Seel's preparation of molecular compounds between $SbCl_5$ and various acid chlorides has been already reported.⁵⁴ K. A. Jensen⁵⁵ has shown that compounds of type $M_2^{II}[SbBr_6]$ are intensely coloured but diamagnetic, probably owing to resonance involving polybromide groupings between neighbouring $[SbBr_6]^{--}$ ions.

The reaction⁵⁶ of bismuth tri-iodide with sodium in liquid ammonia

⁴² *J. Gen. Chem. Russia*, 1942, **12**, 468.

⁴³ W. Lange and R. Livingstone, U.S.P. 2,408,784; W. Lange, U.S.P. 2,408,785.

⁴⁴ *J. Chim. physique*, 1948, **45**, 50.

⁴⁵ See *Ann. Reports*, 1941, **38**, 150; 1943, **40**, 63.

⁴⁶ Ref. 5, p. 210.

⁴⁷ H. Bode, *Z. anorg. Chem.*, 1943, **252**, 113.

⁴⁸ H. Bode and R. Thamer, *Ber.*, 1943, **76**, 121.

⁴⁹ P. Corrieux and A. Gross, *Bull. Soc. chim.*, 1948, **15**, 203.

⁵⁰ H. Margulis, *Compt. rend.*, 1947, **224**, 1730.

⁵¹ G. Weiss, *Bull. Soc. chim.*, 1947, **14**, 476.

⁵² E. Buchholz and H. Viehweger, *Kolloid Beih.*, 1940, **51**, 141.

⁵³ G. O. Doak, *J. Amer. Chem. Soc.*, 1946, **68**, 1991.

⁵⁴ *Ann. Reports*, 1945, **42**, 81.

⁵⁵ *Z. anorg. Chem.*, 1944, **252**, 317.

⁵⁶ G. W. Watt and T. E. Moore, *J. Amer. Chem. Soc.*, 1948, **70**, 1197.

solution gives black, insoluble sodium bismuthide, Na_3Bi , of which the reactions have been described. Hydrolysis ⁵⁷ of Bi^{3+} in water has been shown by e.m.f. measurements to lead to the release of hydrogen ions and the simultaneous formation of polynuclear ions $[\text{Bi}_{n+1}\text{O}_n]^{(n+3)+}$. These are probably sheets, $(\text{BiO})_n^+$ in the limit, with the Bi and the O atoms in a square arrangement, as in bismuth oxyhalides and oxycarbonate. A preparation of potassium and sodium bismuthates from bismuth is described.⁵⁸

Two vanadium arsenides have been described,⁵⁹ VAs and V_2As . Potentiometric study has shown ⁶⁰ that no stable vanadyl cyanides exist in acid solution, and that addition of potassium cyanide to vanadyl salts leads to $\text{VO}(\text{OH})_2$. The various vanadates and niobates obtained by fusion of alkali carbonates and sulphates with vanadium and niobium pentoxide, and by evaporation of lithium metavanadate solution, have been characterised,⁶¹ as also have the vanadates obtained ⁶² by the action of potassium dichromate on vanadyl sulphate. P. Souchay and S. Dubois ⁶³ have studied the degradation of the phospho-12-vanadate ion and deduce that isopolyvanadates are not intermediates in the formation of heteropolyvanadates. They have attempted a classification of complex vanadates of divers types. On heating niobium pentoxide in a stream of hydrogen for several days at $1350\text{--}1700^\circ$ a substance containing about 92% of niobium is obtained. It had been suggested that this was Nb_2O , but G. Brauer ⁶⁴ has now shown that it is Nb_2N , presumably arising from adventitious nitrogen. It has been obtained by heating niobium powder in nitrogen at 1200° to give NbN and reheating this with an equivalent amount of niobium powder, whereupon Nb_2N results. Attempts to produce Nb_2O from NbO and Nb failed.

Group VI.—An electrolytic ozoniser yielding about 12% of ozone at 12° (29% at -13°) has been described.⁶⁵ M. J. S. Dewar ⁶⁶ has proposed a π -complex structure for ozone, which necessitates an acute angle triangular configuration. A. Eucken ⁶⁷ has advanced reasons for supposing that at 0° water contains relatively few simple molecules and consists of $(\text{H}_2\text{O})_2$, $(\text{H}_2\text{O})_4$, and $(\text{H}_2\text{O})_8$ in approximately equal amounts. Dissociation pressures measured up to the melting point of the metal and extrapolated to the boiling point have been given ⁶⁸ for oxides formed on the surface of sixteen metals. Considerable interest continues to be shown in hydrogen peroxide, about which there is still much to be learnt: properties of the

⁵⁷ F. Graner and L. G. Sillén, *Nature*, 1947, **160**, 715.

⁵⁸ S. K. Hagen and L. Mattesen, *Dansk Tidsskr. Farm.*, 1945, **19**, 174.

⁵⁹ A. Morette, *Bull. Soc. chim.*, 1942, **9**, 146.

⁶⁰ L. Ducret, *ibid.*, 1943, **15**, 658.

⁶¹ E. Carrière and H. Guiter, *ibid.*, 1941, **8**, 691, 692, 693.

⁶² F. Rivenq, *ibid.*, 1946, **18**, 677.

⁶³ *Ann. Chim.*, 1948, **3**, 88.

⁶⁴ *Z. Elektrochem.*, 1940, **46**, 397.

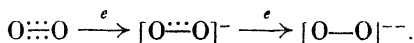
⁶⁵ H. de Boer, *Rec. Trav. chim.*, 1948, **67**, 217.

⁶⁶ *J.*, 1948, 1299.

⁶⁷ *Nach. Ges. Wiss. Göttingen*, 1946, 38.

⁶⁸ B. Lunstman, *Steel Processing*, 1946, **32**, 669.

90% solution have been summarised,⁶⁹ freezing point⁷⁰ and density⁷¹ of aqueous hydrogen peroxide remeasured, and the compound $\text{H}_2\text{O}_2 \cdot 2\text{H}_2\text{O}$, f. p. -50.5° , confirmed, and a gasometric method of determination of the peroxide described which agrees well with potassium permanganate titration, optimum conditions for which are given. In the explosive combination of hydrogen and oxygen, provided the cooling be sufficiently rapid, a condensate containing about 30% of hydrogen peroxide may be obtained⁷³ continuously. Hydrogen peroxide with a 15% water content can be detonated⁷⁴ in steel tubes with walls 3 mm. thick, but not in thin-walled aluminium tubes. Manganese dioxide added to 99.6% hydrogen peroxide produces a non-detonating explosive decomposition. Among the papers dealing with peroxy-salts, M. Haissinsky's⁷⁵ deals with the significance of electronegativities in their formation and other authors have studied⁷⁶ peroxyborates, -carbonates, -vanadates, -molybdates, and -tungstates. W. Kasatoshkin⁷⁷ has found interatomic distances 1.35, 1.27, and 1.20 Å. for $[\text{O}_2]^{--}$, $[\text{O}_2]^-$, and O_2 , which are considered to be consistent with the successive rupture of two three-electron bonds



The equilibria existing between various forms of sulphur and S_2 have been calculated⁷⁸ from published thermal data. Liquid sulphur has been supercooled⁷⁹ in bulk from $115-160^\circ$ to $\sim 50^\circ$ without any essential change in state, and H. Gerding⁸⁰ has shown from Raman spectra that liquid sulphur, up to about 160° , and solutions in carbon disulphide at 18° and in naphthalene at 110° , contain principally S_8 , but that the liquid above 160° contains some other (unknown) species in equilibrium with S_8 . The latter paper reviews Raman spectral determinations carried out in Amsterdam from 1941 to 1946 and concludes also that $\text{H}_2\text{S}_2\text{O}_6$ is probably $\text{SO}(\text{OH})_2 \cdot \text{SO}_3$ rather than $\text{SO}(\text{OH}) \langle \text{O} \rangle \text{SO}(\text{OH})$, that $\text{S}_2\text{O}_5\text{Cl}_2$ is $\text{SO}_2\text{Cl} \cdot \text{O} \cdot \text{SO}_2\text{Cl}$, that SOCl_2 and SeOCl_2 are pyramidal structures, and that

⁶⁹ M. E. Bretschger and E. S. Shanley, *Trans. Electrochem. Soc.*, 1947, **92**, Preprint 36, 487.

⁷⁰ O. Kubaschewski and W. Weber, ref. 5, p. 158.

⁷¹ C. A. Huckaba and F. G. Keyes, *J. Amer. Chem. Soc.*, 1948, **70**, 2578.

⁷² *Idem*, *ibid.*, p. 1640.

⁷³ (Sir) A. C. Egerton and G. J. Minkoff, *Nature*, 1946, **157**, 266.

⁷⁴ L. Médard, *Compt. rend.*, 1946, **222**, 1491.

⁷⁵ *J. Chem. Physics*, 1947, **15**, 152.

⁷⁶ M. Haissinsky and M. Cottin, *Compt. rend.*, 1947, **224**, 392; K. F. Jahn, *Z. Elektrochem.*, 1941, **47**, 810; *Chem. Zentr.*, 1941, I, 184; 1942, II, 511; M. M. Rodriguez, *Anal. Fis. Quim.*, 1944, **40**, 1270; (Mme.) M. E. Rumpf-Nordmann, *Compt. rend.*, 1941, **212**, 485.

⁷⁷ *Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **47**, 193.

⁷⁸ M. Pourbaix, *Bull. Soc. chim. Belg.*, 1945, **53**, 145.

⁷⁹ R. Fanelli, *J. Amer. Chem. Soc.*, 1945, **67**, 1832.

⁸⁰ *J. Chim. physique*, 1948, **45**, 55.

S_2Cl_2 and S_2Me_2 are $X \cdot S \cdot S \cdot X$ and not $S \cdot S < \frac{X}{X}$. Pure sulphur is deposited⁸¹ from solutions in evacuated sealed tubes by the action of bright sunlight, the concentration of the solution having a marked effect on the time of first appearance. The threshold concentration falls appreciably with catalysts; thus, in carbon disulphide and 20 g./l. it decreases to 1 g./l. in the presence of rubrene (a polycyclic hydrocarbon). Other less effective catalysts are known.

The homogeneous reaction between hydrogen and sulphur has been shown⁸² to follow the equation $d[H_2S]/dt = K[H_2][S]^{\frac{1}{2}}(1 + [H_2S][S]^{-1})$ between 350° and 550°. In the presence of α - Ag_2S catalyst between 350° and 420°, rate $= K'[H_2][S]^{-\frac{1}{2}}$. A streaming method was used, and the results accord well with those of E. E. Aynsley, T. G. Pearson, and P. L. Robinson,⁸³ who found, under static conditions, a homogeneous reaction (rate $= K[H_2][S]^{\frac{1}{2}}$, with concentrations which made the $[H_2S]/[S]$ term in the denominator insignificant) and a heterogeneous reaction at the surface of liquid sulphur (rate $= K'A[H_2]$, where A is the area of sulphur surface). Aynsley and Robinson⁸⁴ found a further interesting heterogeneous reaction which takes place on a clean glass surface and continues until a unimolecular layer of hydrogen sulphide is formed thereon. Hydrogen di- and trisulphides^{85a} were prepared and characterised in 1923 and the pentasulphide^{85b} in 1928. Hydrogen polysulphides have been further characterised: ^{85c} H_2S_2, H_2S_3 prepared by a continuous cracking process, H_2S_4, H_2S_5 , and H_2S_6 , from sodium polysulphide solutions. Raman spectra favour chain structures (unbranched) for these⁸⁶ and various organic derivatives.⁸⁷ A xylene-soluble oil, partly volatile, $C_4H_8S_3$, partly non-volatile $C_8H_{16}S_{12}$, and an insoluble polymer have been isolated⁸⁸ from the reaction of ethylene and molten sulphur. M. Goehring⁸⁹ has described hydrolysis and X-ray investigations on N_4S_4 and $H_4N_4S_4$, and similar studies have been made of the sulphur halides and pseudohalides,⁹⁰ the lower sulphur

⁸¹ C. Dufraisse and J. Baget, *Compt. rend.*, 1943, **217**, 693; C. Dufraisse, C. Pinazzi, and J. Baget, *ibid.*, 1946, **222**, 497; C. Pinazzi and J. Baget, *ibid.*, p. 552.

⁸² H. Reinhold, W. Appel, and P. Frisch, *Z. physikal. Chem.*, 1939, **A**, **184**, 273.

⁸³ *J.*, 1935, 58; R. P. Cook and P. L. Robinson, *J.*, 1936, 454.

⁸⁴ *J.*, 1935, 351.

⁸⁵ (a) J. H. Walton and L. B. Parsons, *J. Amer. Chem. Soc.*, 1921, **43**, 2539; (b) H. Mills and P. L. Robinson, *J.*, 1928, 2326; (c) F. Fehér and M. Bandler, *Z. Elektrochem.*, 1941, **47**, 844; *Z. anorg. Chem.*, 1947, **253**, 170; 1947, **254**, 170, 289.

⁸⁶ F. Fehér, *Angew. Chem.*, 1947, **59**, 33.

⁸⁷ J. Donohue and V. Schomaker, *J. Chem. Physics*, 1948, **16**, 92; I. M. Dawson, A. McL. Mathieson, and J. M. Robertson, *J.*, 1948, 322.

⁸⁸ H. E. Westlake, junr., M. G. Mayberry, M. H. Whitlock, J. R. West, and G. J. Harrad, *J. Amer. Chem. Soc.*, 1946, **68**, 748.

⁸⁹ M. Goehring, *Ber.*, 1947, **80**, 110; *Angew. Chem.*, 1944, **57**, 101; ref. 5, p. 193.

⁹⁰ H. Stamm and M. Goehring, *Ber.*, 1943, **76**, 737, 1224; H. Bohme and E. Schneider, *ibid.*, p. 1224; M. Goehring, *ibid.*, p. 742.

oxides⁹¹ and acids H_2SO , $\text{H}_2\text{S}_2\text{O}_3$, H_2SO_2 , $\text{H}_2\text{S}_2\text{O}_4$, and their derivatives.⁹² Therein⁹³ is support for two derivative structures for H_2SO_2 , namely, $\text{H}\cdot\text{SO}\cdot\text{OH}$ and $\text{S}(\text{OH})_2$, while $\text{H}_2\text{S}_2\text{O}_4$ appears to be $\text{HO}\cdot\text{S}\cdot\text{O}\cdot\text{O}\cdot\text{S}\cdot\text{OH}$. The alkali salts of the latter acid may be prepared⁹⁴ by shaking the metal amalgam with pure dry sulphur dioxide at ordinary temperatures.

Thionyl fluoride (b. p. -43.7°) and chlorofluoride (b. p. $+12.3^\circ$) and the fluoride SOF_4 (a colourless offensive gas) have been prepared.⁹⁵ The purification of crude thionyl chloride is effected⁹⁶ by heating under reflux with sulphur which reacts with sulphuryl chloride giving sulphur chlorides which are readily eliminated by fractionation. With ammonia, thionyl-imine is produced⁹⁷ as a colourless liquid monomeric above -85° . At -70° , the vapour pressure is high enough for vacuum distillation, but at -60° a yellow solid polymer forms, as it also does on treatment of the monomer with excess ammonia. Sulphamic acid, $\text{NH}_2\cdot\text{SO}_3\text{H}$, has been prepared⁹⁸ from urea, sulphuric acid, and sulphur dioxide. It melts at 205° , decomposes at 209° , and gives a series of metallic salts;⁹⁹ these, together with the behaviour of the acid with water and phase rule studies¹ with the ammonium salts, have been described. Thallium(I) and ammonium salts of the acid $\text{H}_2\text{SO}_5\text{N}_2$ have been prepared² which are isomorphous with $\text{K}_2\text{SO}_5\text{N}_2$, and X-ray diffraction shows the ion $[\text{SO}_3\cdot\text{N} \leq \text{N}=\text{O}]^{--}$ (XI), for which theoretical valency explanations are advanced.³ A method of freeing sulphuric acid of last traces of nitrogen is described.⁴

Conductometric titration of solutions of sodium sulphate, chromate, molybdate, and tungstate with sodium hydroxide suggests⁶ the existence of the ortho-acids H_6XO_6 in every case. Ortho-acids are, however, not indicated by the similar titration of sodium sulphite and thiosulphate.

Selenium has received little attention; hydrogen deuterium selenide, HDSe , has been prepared;⁷ the photo-oxidation of hydrogen selenide has

⁹¹ H. Stamm and K. D. Wiebusch, *Naturwiss.*, 1944, **32**, 42; ref. 5, p. 179; P. W. Schenk, *Chem.-Ztg.*, 1943, **67**, 251.

⁹² G. Rienäcker and F. Gesser, ref. 5, p. 126; H. Stamm and M. Goehring, *Angew. Chem.*, 1945, **58**, 52; M. Goehring, *Ber.*, 1948, **80**, 219.

⁹³ *Idem*, *Naturwiss.*, 1944, **32**, 42. ⁹⁴ L. Rougeot, *Compt. rend.*, 1946, **222**, 1497.

⁹⁵ J. Soll and W. Kwasnik, ref. 5, p. 192; I. G. Leverkusen, Patentanmeldung, R. 100449.

⁹⁶ D. L. Cottle, *J. Amer. Chem. Soc.*, 1946, **68**, 1380.

⁹⁷ P. W. Schenk, *Ber.*, 1942, **75**, 94.

⁹⁸ J. W. Leonard, U.S.P. 2,409,572; E. J. Tauch, U.S.P. 2,408,492; 2,408,823.

⁹⁹ F. Oberhauser B. and H. E. Urbina C., *Anales fac. fil. y educ., Univ. Chile, Sección quim.*, 1946, **3**, 109, 119; *Chem. Abs.*, 1947, **41**, 1944.

¹ J. H. Thelin and P. A. van der Meulen, *J. Amer. Chem. Soc.*, 1948, **70**, 1796; S. H. Laning and P. A. van der Meulen, *ibid.*, p. 1799.

² E. G. Cox, G. A. Jeffrey, and H. P. Stadler, *Nature*, 1948, **162**, 770; J. Perouze, *Annalen*, 1835, **15**, 240.

³ M. G. Evans and J. Gergely, *Nature*, 1948, **162**, 770.

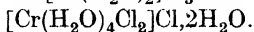
⁴ B. V. Ramachandran, *ibid.*, p. 450.

⁶ L. J. Olmer and F. Fouasson, *Compt. rend.*, 1946, **222**, 1398.

⁷ A. Krius, *Z. physikal. Chem.*, 1941, **B**, **48**, 321.

been shown⁸ to require the presence of liquid water and to be autocatalysed by solid selenium; the vapour pressure of selenium dioxide has been measured⁹ and its chain structure confirmed (see above),⁸⁰ $\cdot\text{O}\cdot\text{SeO}\cdot\text{O}\cdot\text{SeO}\cdot$. E. Montignie¹⁰ has summarised the chemical properties of tellurium and its compounds, especially the tellurites.¹¹ Conductometric titration of telluric acid solutions with sodium hydroxide shows¹² four changes of slope corresponding to the neutralisation of 1, 2, 4, and 6 mols. of hydroxide per mol. of TeO_3 . It is concluded that the acid functions as H_6TeO_6 (cf. S, Cr, Mo, and W above⁶).

A hitherto unknown stable isotope of polonium has been found¹³ in certain Roumanian tellurium minerals. Previous conclusions on the reducibility of dichromium trioxide by hydrogen are not confirmed,¹⁴ and previous observation of a greater release of water on heating in hydrogen than in nitrogen alone is now thought to be due to the more rapid drying of the oxide in hydrogen. In confirmation of this conclusion, no Cr or CrO has been detected. R. Lautié¹⁵ has, however, obtained the Group VIA metals and vanadium by partial reduction of the oxide with carbon monoxide, or light paraffins, at 400–500° and then treating the product with hydrogen or ammonia at >700°. Work on chromium(II) iodide and hydrazine complexes has been reported.¹⁶ Polarographic study¹⁷ has shown that violet chromium(III) sulphate contains $[\text{Cr}(\text{H}_2\text{O})_6]^{3+}$ while the green sulphate contains $[\text{Cr}(\text{H}_2\text{O})_4\text{SO}_4]^+$. Similar considerations¹⁸ apply to hydrated chromium(III) chloride, violet $[\text{Cr}(\text{H}_2\text{O})_2]\text{Cl}_3$ and dark green



Vapour-pressure measurements¹⁹ have been made on aged chromium(III) salt solutions and indicated equilibrium between the violet and green complexes. The thermal stabilities of a number of chromium(III) complexes have been investigated,²⁰ as also the suitability of various such complexes for the electrodeposition of chromium.²¹

W. D. Treadwell and Y. Schaepfi²² have proposed a constitutional

⁸ D. J. G. Ives and R. W. Pittman, *J.*, 1948, 766.

⁹ A. G. Amelin and M. I. Beljakov, *J. Physical Chem. Russia*, 1944, **18**, 466.

¹⁰ *Bull. Soc. chim.*, 1948, **15**, 180.

¹¹ *Ibid.*, 1940, **7**, 681.

¹² F. Fouasson, *Compt. rend.*, 1946, **222**, 958; *Ann. Chim.*, 1948, **3**, 594.

¹³ H. Hulubei and (Mlle.) Y. Cauchois, *Compt. rend.*, 1940, **210**, 761; 1947, **224**, 1285.

¹⁴ P. Pascal, *Bull. Soc. chim.*, 1945, **12**, 627.

¹⁵ *Ibid.*, 1940, **7**, 961.

¹⁶ F. Hein and G. Bahr, *Z. anorg. Chem.*, 1943—44, **252**, 55; see also *Ann. Reports*, 1945, **42**, 75.

¹⁷ J. B. Willis, *J. Proc. Roy. Soc. New South Wales*, 1946, **78**, 239.

¹⁸ D. S. Datar and D. R. Kulkarni, *Current Sci.*, 1946, **15**, 251.

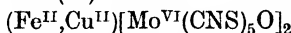
¹⁹ N. O. Smith, *J. Amer. Chem. Soc.*, 1947, **69**, 91.

²⁰ T. D. O'Brien and J. C. Bailar, junr., *ibid.*, 1945, **67**, 1856.

²¹ R. W. Parry, S. Swann, junr., and J. C. Bailar, junr., *Trans. Electrochem. Soc.*, 1947, **92**, Preprint 27, 311.

²² *Helv. Chim. Acta*, 1946, **29**, 771.

formula for molybdenum-blue, empirically Mo_6O_{17} ($= \text{Mo}_2\text{O}_5, 4\text{MoO}_3$), which explains the deep colour and other properties of the material. The existence of hexanuclear molybdenum(II) complexes containing $[\text{Mo}_6\text{Cl}_8]^{++}$ has been reported.²³ A molybdic acid solution in the presence of alkali thiocyanates gives²⁴ an orange colour, soluble in *iso*amyl alcohol, with Fe^{++} or Cu^{++} or on addition of tin(II) chloride. The formation of



and $\text{Mo}^{\text{III}}[\text{Mo}^{\text{VI}}(\text{CNS})_5\text{O}]_3$ is indicated, the colour residing in the anion. WOF_2 and WF_4 have been prepared :²⁵ the first a grey solid compacting to shiny black flakes, as graphite, and chemically very inert, and the second a reddish-brown hygroscopic solid, hydrolysed by hot alkalis to hydrated WO_2 . A considerable number of papers are available dealing with molybdates and heteropoly-molybdates and -tungstates, and it still appears possible to interpret results in this very complicated field in fairly arbitrary manner. J. Byé²⁶ concludes that dilute solutions of molybdic acid contain the single strong acid $\text{H}_2\text{Mo}_4\text{O}_{13}$ and that in more concentrated solutions $\text{H}_4\text{Mo}_6\text{O}_{20}$ or derived ions are present. Y. Doucet and G. Carpéni find,²⁷ on re-examination of results separately obtained²⁸ and variously interpreted, that the species involved approximate to the following :

| MoO_3 concn. | Species. | MoO_3 concn. | Species. |
|-----------------------|---|-----------------------|--|
| 0.2—0.1M. | $\text{H}_2[\text{Mo}_{16}\text{O}_{49}]$ | 0.04—0.002M. | $\text{H}_2[\text{Mo}_4\text{O}_{13}]$ |
| 0.1—0.04M. | $\text{H}_2[\text{Mo}_8\text{O}_{25}]$ | <0.002M. | $\text{H}_2[\text{MoO}_4]$ |

Similar conclusions emerge for tungstic acids.

(Mme.) H. Frey,²⁹ investigating aqueous solutions of sodium molybdate conductimetrically, concludes that species reported to contain more than two molybdenums per molecule are probably mixtures of Na_2MoO_4 , NaHMo_2O_7 , and $\text{Na}_2\text{Mo}_2\text{O}_7$. The composition of ammonium molybdate crystallising from solution at pH between 0.3 and 10.4 has been found³⁰ to range between $(\text{NH}_4)_2\text{O}, 10\text{MoO}_3, 4\text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{O}, \text{MoO}_3$, but these results have not been interpreted in terms of the ionic species involved. P. Souchay³¹ has described a cryoscopic method for investigating complex anions and has applied it to selenito-, sulphito-, and methylarsinato-molybdates among others. Salts of ethylenediamino- and pyridino-copper, -silver, -nickel, and -mercury cations with heteropoly-tungstate and -molybdate,³²

²³ C. Brosset, *Arkiv Kemi, Min. Geol.*, 1945, A, 20, No. 7; see also *Ann. Reports*, 1946, 43, 95.

²⁴ A. T. Dick and J. B. Bingley, *Nature*, 1946, 158, 516.

²⁵ H. F. Priest and W. C. Schumb, *J. Amer. Chem. Soc.*, 1948, 70, 3378.

²⁶ *Ann. Chim.*, 1945, 20, 463.

²⁷ *Compt. rend.*, 1947, 224, 1719; G. Carpéni, *Bull. Soc. chim.*, 1947, 14, 484, 490, 492, 501.

²⁸ *Idem*, *Compt. rend.*, 1947, 224, 1060; Y. Doucet, *ibid.*, p. 1361.

²⁹ *Ibid.*, 1940, 211, 503.

³⁰ H. Guiter, *Bull. Soc. chim.*, 1945, 12, 74.

³¹ *Ibid.*, 1948, 15, 143.

³² M. Jean, *Compt. rend.*, 1946, 223, 155.

conditions of stability³³ of phospho-3-tungstates and phospho-11-tungstates, the absorption spectra³³ of tungstates, phosphates, isopolytungstates, and phosphotungstates, analytical applications³⁴ and other physicochemical studies³⁵ of phospho-, germano-, and silico-molybdic and -tungstic acids have been described.

Group VII.—A useful account of Moissan's life (1852—1907) and the isolation of fluorine in 1886 was given by K. R. Webb,³⁶ and there is the report³⁷ of an important symposium on fluorine chemistry held in Chicago in 1947. This comprehensive survey deals with generation, handling, and disposal of fluorine, the development on an industrial scale of fluorocarbon processes, and the chemistry of the element and its compounds. Of particular interest here are a small-scale, 250-ampère, electrolytic cell suitable for laboratory purposes, the preparation and properties of sulphur hexafluoride, the vapour pressure of hydrogen fluoride solutions, the systems $\text{HF-H}_2\text{O}$ and $\text{HF-H}_2\text{SiF}_6\text{-H}_2\text{O}$, and the use of fluorine in the hydrogen-fluorine torch. Further reviews deal with the preparation, structure, and properties of non-metal fluorides³⁸ and of the halogen fluorides.³⁹ The inter-halogen compounds ClF , ClF_3 ^{40, 42} ($= \text{Cl}_2\text{F}_6$), BrF_3 ,⁴¹ and BrF_5 ⁴² are variously studied with regard to preparation, heats of formation, and dissociation absorption spectra. ClO_2F (m. p. -115° , b. p. -6°) has been prepared⁴³ by reaction between fluorine and chlorine dioxide diluted with nitrogen at -50° , and FCIO_4 ("fluorine perchlorate") was obtained⁴⁴ as a colourless explosive liquid (b. p. $-15.9^\circ/755$ mm., f. p. -167.3°) when fluorine was passed over 72% perchloric acid in a platinum boat. Fluorination of solid $\text{HIO}_4 \cdot 2\text{H}_2\text{O}$, of solid potassium periodate, and of aqueous and sulphuric acid solutions of periodic acid does not, however, lead⁴⁵ to the formation of fluorine periodate. Dielectric-constant measurements on hydrogen fluoride vapour indicate⁴⁶ polar, and therefore more or less linear, polymers, in agreement with X-ray and electron-diffraction data. That the association factors indicated by dipole moment are less than those calculated from vapour density suggests that cyclic structures do not con-

³³ S. Dubois and P. Souchay, *Ann. Chim.*, 1948, **3**, 105.

³⁴ M. Jean, *ibid.*, p. 470.

³⁵ R. Ripan and C. Lleanu, *Compt. rend.*, 1947, **224**, 196; P. Souchay and A. Tchakirian, *Ann. Chim.*, 1946, **1**, 232, 249; P. Souchay, *ibid.*, 1945, **20**, 73, 96.

³⁶ *Chem. and Ind.*, 1946, 306.

³⁷ *Ind. Eng. Chem.*, 1947, **39**, 236.

³⁸ L. M. Dubnikov, *Uspekhi Khim.*, 1947, **16**, 189.

³⁹ H. S. Booth and J. T. Pinkston, junr., *Chem. Reviews*, 1947, **41**, 421.

⁴⁰ E. Wicke, *Nach. Ges. Wiss. Göttingen*, 1946, 89; L. Domange and J. Neudorffer, *Compt. rend.*, 1948, **226**, 920; H. Schmitz and H. J. Schumacher, *Z. Naturforsch.*, 1947, **2a**, 359, 362, 363.

⁴¹ P. H. Brodersen and H. J. Schumacher, *ibid.*, p. 358.

⁴² W. Kwasnik, ref. 5, p. 168; German Patents, J.76585, J.76482.

⁴³ H. Schmitz and H. J. Schumacher, *Z. anorg. Chem.*, 1942, **249**, 238.

⁴⁴ G. H. Rohrbach and G. H. Cady, *J. Amer. Chem. Soc.*, 1947, **69**, 677.

⁴⁵ *Idem*, *ibid.*, 1948, **70**, 2603.

⁴⁶ R. A. Oriana and C. P. Smyth, *ibid.*, p. 125; H. A. Benesi and C. P. Smyth, *J. Chem. Physics*, 1947, **15**, 337; see *Ann. Reports*, 1943, **40**, 61.

tribute appreciably to the dipole moment. Results thus favour successive equilibria $\text{HF} + (\text{HF})_n \rightleftharpoons (\text{HF})_{n+1}$ rather than the single equilibrium $6\text{HF} \rightleftharpoons \text{cyclic } (\text{HF})_6$.

A partial separation of ^{35}Cl and ^{37}Cl has been made⁴⁷ by means of a Clusius-Dickel separation, modified to employ two coaxial Pyrex cylinders. Sufficient chlorine containing 45% of ^{37}Cl was obtained for the spectrographic determination of the nuclear spin of ^{37}Cl . The preparation of chlorine dioxide by electrolytic or chemical reduction of chlorates has been the subject of a number of patents.⁴⁸ Pure chlorine passed over ferric oxide gives⁴⁹ solely ferric chloride and oxygen and the reaction is rapid at 700–1000°. Chlorination is accelerated by the presence of carbon. Tungstic oxide is also attacked by chlorine at the same temperature to give WO_2Cl_2 . Alumina, silica, and titania, however, are not attacked even in the presence of carbon up to 800° and a separation is thus readily obtained. The stability, hydrolysis, and polymerisation of cyanogen chloride have been investigated.⁵⁰ P. Pierron⁵¹ has described the preparation of solid hypochlorites by shaking solid Ca, Sr, Na, or Li hydroxides with dichlorine monoxide in carbon tetrachloride and evaporating in a vacuum. These, and silver hypochlorites, are stable whereas sodium hypochloride is unstable. With excess of the oxide there is a further reaction to perchlorate: $\text{M}(\text{OCl})_2 + 6\text{Cl}_2\text{O} \longrightarrow \text{M}(\text{ClO}_4)_2 + 6\text{Cl}_2$.

K. Clusius⁵² has reported that bromine at -252° is orange and not colourless. Procedure has been described⁵³ for obtaining radioactive iodine, and R. Daudel⁵⁴ has summarised the uses to which he and his collaborators have put this particular tracer in work in exchange reactions, the structure of $[\text{HgI}_4]^{--}$, velocity coefficients of ionic dissociation, *e.g.*, $[\text{HgI}_4]^{--} \rightleftharpoons \text{Hg}^{++} + 4\text{I}^-$, and the origin of iodine produced in the periodate-iodide reaction. J. Kleinberg and A. E. Davidson⁵⁵ have recently reviewed the more significant studies concerning the nature of violet and brown iodine solutions. Molecular-weight determinations indicate that the iodine is diatomic in all solutions, but other behaviour suggests that the brown solutions contain free iodine in equilibrium with iodine chemically bound to the solvent. G. Kortüm and G. Friedheim⁵⁶ have concluded similarly that the colour differences are probably due to different intermolecular forces between solute and solvent and not to differences in the degree of dispersion of the dissolved iodine. Evidence of absorption spectra of

⁴⁷ E. F. Shrader, *Physical Rev.*, 1946, **69**, 439.

⁴⁸ S. H. Persson, B.P. 581,931; Swed.P. 116,363; W. S. Hutchinson, U.S.P. 2,409,862.

⁴⁹ A. Chrétien and P. Galmiche, *Compt. rend.*, 1946, 802; P. Galmiche, *Ann. Chim.*, 1948, **3**, 243.

⁵⁰ A. B. Van Cleave and H. E. Mitton, *Canadian J. Res.*, 1947, **25**, B, 4430; A. B. Van Cleave and R. L. Eager, *ibid.*, 1947, **25**, F, 284.

⁵¹ *Bull. Soc. chim.*, 1941, **8**, 660, 664.

⁵² *Z. Naturforsch.*, 1947, **2b**, 244.

⁵³ O. Erbacher and M. Beck, *Z. anorg. Chem.*, 1944, **252**, 357.

⁵⁴ *J. Chim. physique*, 1944, **41**, 49.

⁵⁵ *Chem. Reviews*, 1948, **42**, 601.

⁵⁶ *Z. Naturforsch.*, 1947, **2a**, 20.

solutions in benzene, toluene, xylene, mesitylene, and methylnaphthalene favours a donor-acceptor mechanism, and iodine in brown solution appears to be slightly more reactive than presumably free iodine in the violet solutions. Kleinberg and Davidson have shown that no correlation exists between solvent dielectric constant and colour (solutions in solvents CHCl_3 , $\text{CH}_2\text{Br}\cdot\text{CH}_2\text{Br}$, $\text{CHCl}_2\cdot\text{CH}_3$, and $\text{CHCl}\cdot\text{CHCl}$, having considerable dipole, are violet as in non-polar CCl_4) and F. Fairbrother⁵⁷ has suggested that the electron-donor character of the solvent is the determining factor. This would be so if, as Fairbrother suggests, the proximity of such an electron donor to an iodine molecule stabilises one of the ionic canonicals I^+I^- , where I^+ has an unoccupied $5p$ orbital, in resonance with I_2 , thereby destroying the symmetry and altering the absorption spectrum.

Parachor, rheochor, and molar refraction measurements indicate⁵⁸ that iodic acid contains the species, $(\text{HIO}_3)_3 \xrightarrow{0.1 \text{ N}} (\text{HIO}_3)_2 \xrightarrow{0.04 \text{ N}} \text{HIO}_3 \longrightarrow \text{H}^+ + \text{IO}_3^-$. Magnetic studies⁵⁹ of periodic acid and the periodates of Na, Ag, Hg, La, Cu, Ni, Co, Y, and Ce suggest that the acid exists both in solution and in the solid state as $\text{HIO}_4\cdot 2\text{H}_2\text{O}$ and that the salts are true periodates (salts of HIO_4 , H_3IO_5 , H_5IO_6 , $\text{H}_4\text{I}_2\text{O}_9$, $\text{H}_8\text{I}_2\text{O}_{11}$, and $\text{H}_{12}\text{I}_2\text{O}_{13}$ appear from the found compositions), none of them being complex. Manganese carbide, Mn_3C , has been hydrolysed⁶⁰ with water to yield methane, ethane, and other low alkanes; and with hydrogen chloride to give carbon, hydrogen, and liquid hydrocarbons. The reaction between manganese dioxide and sodium oxide in fused sodium nitrite gives⁶¹ a compound crystallising from concentrated aqueous sodium hydroxide as $\text{Na}_2\text{MnO}_4\cdot 10\text{H}_2\text{O}$, which contains quinquevalent manganese with characteristic blue tint and forms mixed crystals with sodium phosphate, arsenate, and vanadate. Warming induces disproportionation to MnO_2 and Mn^{6+} ; in concentrated alkaline solution the equilibrium $\text{Na}_2\text{Mn}^{\text{VII}}\text{O}_4 + \text{MnO}_2 + 4\text{NaOH} \rightleftharpoons 2\text{Na}_3\text{Mn}^{\text{V}}\text{O}_4 + 2\text{H}_2\text{O}$ obtains. The chemistry of technetium adsorbed on rhenium sulphide or copper sulphide has been described.⁶²

K. A. Jensen⁶³ has shown K_2ReI_6 to be paramagnetic, in agreement with the theory for Re^{IV} . The reduction of Re^{VII} to Re^{IV} by chromium(II) chloride and conditions under which Re^{V} can be stabilised are described.⁶⁴ Per-rhenates can be prepared⁶⁵ by burning rhenium to Re_2O_7 , hydrolysis to HReO_4 , and treating this with metal oxide or carbonate: Li, Na, K, NH_4 , Rb, and Cs salts are thoroughly characterised (all white).

Group VIII.—Iron and cobalt hydrides have been prepared⁶⁶ by the

⁵⁷ *Nature*, 1947, **160**, 87; *J.*, 1948, 1051.

⁵⁸ M. R. Nayar and L. N. Srivastava, *Phil. Mag.*, 1948, **39**, 800.

⁵⁹ S. L. Aggarwal and S. Singh, *J. Indian Chem. Soc.*, 1945, **22**, 158; R. C. Sahney, S. L. Aggarwal, and S. Singh, *ibid.*, 1946, **23**, 177; 1947, **24**, 193.

⁶⁰ W. R. Myers and W. P. Fishel, *J. Amer. Chem. Soc.*, 1945, **67**, 1962.

⁶¹ H. Lux, *Z. Naturforsch.*, 1946, **1**, 281.

⁶² E. Jacobi, *Helv. Chem. Acta*, 1948, **31**, 2118. ⁶³ *Z. anorg. Chem.*, 1944, **252**, 307.

(Mlle.) S. Tribalat, *Compt. rend.*, 1946, **292**, 1388.

⁶⁴ W. T. Smith, junr., and S. H. Long, *J. Amer. Chem. Soc.*, 1948, **70**, 354.

⁶⁵ R. C. Ray and R. B. N. Sahai, *J. Indian Chem. Soc.*, 1946, **23**, 61, 67.

reactions between phenylmagnesium bromide and the respective chlorides in ethereal solution in the presence of hydrogen. Ferrous chloride gives FeH_2 and ferric chloride gives FeH_3 , both decomposed by water and alcohol, and dissociated at about 58° into FeH , which at higher temperatures yields iron. Cobalt and nickel hydrides have similar properties as regards dissociation: $\text{XH}_2 \longrightarrow \text{XH} \longrightarrow \text{X}$. A thermomagnetic and X-ray study⁶⁷ of the superficial oxidation of iron has revealed that the rate of oxidation increases with rise in temperature, but the degree of oxidation of the products decreases. Hence the film formed at 900° is almost entirely ferrous oxide. Oxidation occurs by a diffusion of iron through the oxide film to the air-film interface. A film formed at 900° and then detached from the underlying metal becomes transformed almost completely into ferric oxide when again placed in air at 900° . Thin plates of iron when oxidised at 900° until no free metal remains yield films consisting of a mixture of Fe_2O_3 and Fe_3O_4 . Thermal combination⁶⁸ of iron(III) oxide and phosphoric oxide in various ratios has yielded the phosphates $\text{Fe}(\text{PO}_3)_3$, FePO_4 , $\text{Fe}_4(\text{P}_2\text{O}_7)_2$, and $\text{Fe}_7\text{P}_3\text{O}_{18}$ as indicated by composition, X-ray, ultra-violet reflection spectra, and magnetic susceptibility. R. S. Nyholm⁶⁹ has prepared polynuclear complexes of iron(III) containing chlorine-bridge links and coordinated arsine derivatives.

Potentiometric study⁷⁰ of the oxidation of nickel, cobalt, and manganese(II) hydroxides shows that $\text{Ni}(\text{OH})_2$ is oxidised completely to Ni_2O_3 by sodium hypochlorite, hypobromite, and peroxydisulphate, slightly only by sodium periodate and potassium permanganate, and incompletely to Ni_3O_4 by sodium hypoiodite, ozone, and hydrogen peroxide. Cobalt(II) hydroxide is incompletely oxidised to CoO_2 (some Co_2O_3) by sodium hypochlorite, -bromite, or iodite, - sodium peroxydisulphate, and potassium permanganate; hydrogen peroxide gives a mixture of Co_2O_3 and Co_3O_4 . Manganese(II) hydroxide is converted completely into the dioxide by all these reagents except hydrogen peroxide, which effects only partial oxidation.

In propyl alcohol and acetone solution anhydrous cobalt(II) chloride is probably⁷¹ chlorocobalt(+1) trichlorocobaltate(-1), $[\text{CoCl}][\text{CoCl}_3]$, giving lithium trichlorocobaltate(-1) on treatment with lithium chloride. Hydration then probably leads to $[\text{CoCl}_2]_2 \cdot 6\text{H}_2\text{O}$, *i.e.*, $[\text{CoCl}(\text{H}_2\text{O})_3][\text{CoCl}_3(\text{H}_2\text{O})_3]$. R. A. Robinson and J. B. Brown,⁷² however, deduce from vapour-pressure measurements on cobalt(II) chloride and nitrate, with and without added lithium or calcium chloride, that the change in colour rose to red in the presence of chloride is due to $[\text{Co}(\text{H}_2\text{O})_6]^{++} + 2\text{Cl}^- \longrightarrow [\text{CoCl}_2 \cdot 4\text{H}_2\text{O}]$

⁶⁷ (Mme.) A. Michel, J. B. Bénard, and G. Chaudron, *Bull. Soc. chim.*, 1944, 11, 175.

⁶⁸ P. Brasseur, *ibid.*, 1946, 13, 261, 436.

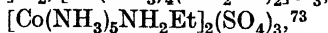
⁶⁹ J. Proc. Roy. Soc. New South Wales, 1944, 78, 229.

⁷⁰ J. Besson, *Compt. rend.*, 1946, 223, 288.

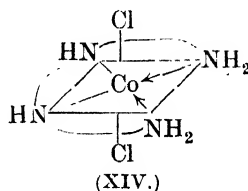
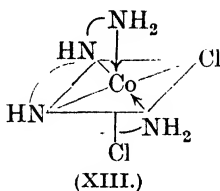
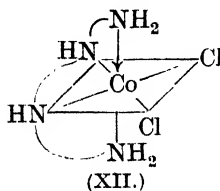
⁷¹ (Mlle.) Y. Wormser, *Bull. Soc. chim.*, 1948, 15, 395.

⁷² *Trans. Roy. Soc. New Zealand*, 1948, 77, 1.

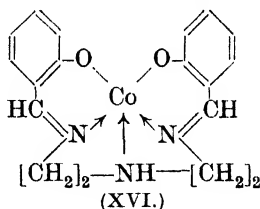
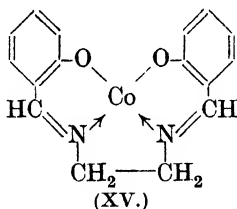
(undissociated) + 2H₂O. Considerable work has been done on other cobalt complexes: [CoCl en₂py]Cl₂, [Co(NH₃)₄(NH₂Me)₂]Cl₃,



a *cis*- and *trans*-diguano-cobalt(III) complex series,⁷⁴ nitritopentammino-cobalt(+2) nitrate, [Co(NH₃)₅(ONO)](NO₃)₂ and its isomerisation kinetics,⁷⁵ a series⁷⁶ of quaternary arsonium salts containing the tetrathiocyanato-cobaltate(-2) anion, and glyoximocobalt(III) polysulphides⁷⁷ (discussed below with the rhodium compounds) have been severally described or discussed. The co-ordination of compounds NH₂·[CH₂]_n·NH₂ with cobalt(III) has been found⁷⁸ to occur, and the product is described where *n* = 3 but not where *n* = 6 or 10. F. Basolo⁷⁹ has described a series of cobalt(III) complexes with the quadridentate triethylenetetrammine. A *cis*-configuration (XII) or (XIII) is inferred from a comparison with *cis*-dichlorotetrammines and *cis*-dichloroethylenediammines: no *trans*-(XIV) series could be obtained.



An important series⁸⁰ of papers has recently appeared on synthetic chelate compounds comprising a metal (usually cobalt), an aldehyde or ketone (*e.g.*, salicylaldehyde derivative), and an amine; *e.g.*, (XV) and



(XVI). These are capable of carrying oxygen as loose molecular compounds [(XV) carries one molecule of O₂ per two Co atoms; (XVI) one

⁷³ (Mlle.) J. Brigando, *Compt. rend.*, 1947, **225**, 1319.

⁷⁴ P. Ray and A. N. Majunbar, *J. Indian Chem. Soc.*, 1946, **23**, 73.

⁷⁵ B. Adell and G. Tholin, *Acta Chem. Scand.*, 1947, **1**, 624.

⁷⁶ F. P. Dwyer, N. A. Gibson, and R. S. Nyholm, *J. Proc. Roy. Soc. New South Wales*, 1945, **79**, 118.

⁷⁷ L. Malatesta, *Gazzetta*, 1942, **72**, 484.

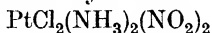
⁷⁸ J. C. Bailar and J. B. Work, *J. Amer. Chem. Soc.*, 1946, **68**, 232.

⁷⁹ *Ibid.*, 1948, **70**, 2634.

⁸⁰ M. Calvin, *Chem. Products*, 1947, **10**, 19; M. Calvin, R. H. Bailes, W. K. Wilmarth, C. H. Barkeley, S. Avanoft, and E. W. Hughes, *J. Amer. Chem. Soc.*, 1946, **68**, 2254, 2257, 2263, 2267, 2273; O. L. Hark and M. Calvin, *ibid.*, p. 2612; see also G. C. Harrison, H. Diehl, C. C. Haach, L. M. Liggett, and R. J. Brouns, *Iowa State Coll. J. Sci.*, 1947, **21**, 311, 316, 326, 335.

molecule of O_2 per one Co atom] and in this respect resemble hæmoglobin. The six papers treat: (a) general results of the investigation on oxygen-carrying chelates of this type, (b) rates of oxygenation, (c) oxygen production, (d) magnetic properties, (e) equilibria of the type, 2 chelate (solution) + $O_2(g) \longrightarrow$ chelate, O_2 (solution), and (f) similar equilibria involving type (XVI) compounds in which groups Cl, F, OPh, NO_2 , or H occupy the position *ortho* to the oxygen in the benzene nuclei. Raman spectral investigation of nickel carbonyl confirms⁸¹ a tetrahedral structure; tetracyanonickelates(−2) of beryllium, zinc, cadmium, gallium, thallium, and neodymium have been described.⁸² A number of thiols,⁸³ $R \cdot SH$, form diamagnetic complexes with nickel, which are probably highly polymerised, perhaps $Ni(SR)_2 \cdot Ni(SR)_2 \cdot Ni(SR)_2$.

Pure platinum has been prepared⁸⁴ by converting the metal first into K_2PtCl_6 , then into $K_2Pt(NO_2)_4$, which with 20% ammonia gives $Pt(NH_3)_2(NO_2)_2$: this is oxidised by chlorine to Blomstrand's salt



which after recrystallisation from water is heated to give metallic platinum. Spectrally pure platinum is produced even when the original metal contains 25% of palladium. I. I. Tscherniaev⁸⁵ has described further reactions of Blomstrand's salts. The suggestion by A. D. Walsh has already been reported⁸⁶ that the platinum-olefin complexes can be regarded as "π-complexes" of the type put forward by M. J. S. Dewar,⁸⁷ where a dative molecular bond, or "π-bond," is formed by donation of the π electron of the olefin. Support for the suggestion is given by L. Bateman⁸⁸ and by A. E. A. Werner,⁸⁹ the former pointing out that the heats of formation of similar complexes of $CH_3 \cdot CH : CH \cdot C_2H_5$ and of cyclohexene with aqueous silver nitrate are approximately half those for the formation of analogous amines and that the proton affinity of ethylene (174 kcal./mole) is only 10 kcal. less than that of water.

It remains only to mention a few papers which add to the complex chemistry of Group VIII reported⁹⁰ in 1946. Complex compounds of platinum with phosphine and derivatives of phosphorous acid have been prepared.⁹¹ The isomerisation and dimerisation of Peyronet's salt, $Pt(NH_3)_2Cl_2$, have been investigated.⁹² D. P. Mellor and J. B. Willis⁹³ have contributed

⁸¹ B. L. Crawford and W. Horwitz, *J. Chem. Physics*, 1948, **16**, 147.

⁸² T. Karantassis and P. Sakellarides, *Compt. rend.*, 1947, **224**, 1640.

⁸³ K. A. Jensen, *Z. anorg. Chem.*, 1944, **252**, 227.

⁸⁴ I. I. Tscherniaev and A. M. Rubinstein, *Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **48**, 332.

⁸⁵ *Bull. Acad. Sci. U.R.S.S., Classe Sci. Chim.*, 1945, **3**, 203.

⁸⁶ *Ann. Reports*, 1946, **43**, 122.

⁸⁷ *Nature*, 1945, **176**, 784; *J.*, 1946, 406, 707; Faraday Soc. Discussions, 1947, **2**, 50.

⁸⁸ *Nature*, 1947, **160**, 56. ⁸⁹ *Ibid.*, p. 644. ⁹⁰ *Ann. Reports*, 1946, **43**, 120.

⁹¹ A. A. Grenberg, S. A. Razumova, and A. D. Troitzkaja, *Bull. Acad. Sci. U.R.S.S., Sér. Chim.*, 1946, **3**, 253.

⁹² A. M. Rubinstein and L. F. Vereschtschaguine, *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **54**, 697.

⁹³ *J. Proc. Roy. Soc. New South Wales*, 1946, **79**, 141.

further to the knowledge of the square complexes of platinum, palladium, and nickel in which steric hindrance involves considerable distortion from the planar structure. Dimethylglyoximorhodium polysulphides⁹⁴ have been described, analogous to the cobalt compounds mentioned above.⁷⁷ Both are formed by the treatment of the metal chloride and dimethylglyoxime in aqueous alcohol with ammonium or sodium polysulphide. If sodium polysulphide is used for the cobalt compound some amine or ammonia must be present otherwise cobalt sulphide is quantitatively precipitated. The compounds are probably polymeric containing $[M^{III}R_2]^+$ units joined together by S_3 , S_4 , or S_5 chains in the case of the cobalt, and S_6 chains in the case of the rhodium compound (R represents $OH\cdot N\cdot CMe\cdot CMe\cdot NO\cdot$). Finally, F. P. J. Dwyer and R. S. Nyholm⁹⁵ have prepared and isolated a complex of quadrivalent rhodium in the green insoluble $Cs_3Rh^{IV}Cl_6$ formed by oxidation of a fine pink suspension of $Cs_3Rh^{III}Cl_6$ by a solution of caesium nitrate in dilute nitric acid. The face-centred cubic structure of Cs_2RhCl_6 is isomorphous with $(NH_4)_2PtCl_6$.

Lanthanons and Actinons.*—A greatly simplified treatment of monazite has been described by F. R. Hartley and A. W. Wylie.⁹⁶ The direct chlorination at $700\text{--}750^\circ$ of monazite, briquetted with wood charcoal, has the advantages that phosphorus is directly volatilised as $POCl_3$, which can be condensed to serve as a reaction indicator, that other impurities are largely eliminated as volatile chlorides, and that anhydrous lanthanon chlorides are directly obtained. Approximately the reaction is: $MPO_4 + 3C + 3Cl_2 \rightarrow MCl_3 + POCl_3 + 3CO$.

S. Takvorian⁹⁷ has further considered the separation of ceric lanthanons, complex compounds of lanthanons with antipyrine and pyramidon have been described,⁹⁸ and a dilatometric investigation⁹⁹ of cerium oxides suggests that the blue oxide Ce_4O_7 is a salt-like oxide and not a mixed oxide, $2CeO_2\cdot Ce_2O_3$. D. C. Hess¹ has investigated isotopic abundances in Eu, Gd, and Tb and calculated atomic weights therefrom:

| | | International value. | Isotopes ($>0.02\%$). |
|----------|--------|-------------------------|-----------------------------------|
| Eu | 151.97 | 152.0 | 151 and 153 |
| Gd | 157.26 | 156.9 | 152, 154, 155, 156, 157, 158, 160 |
| Tb..... | 158.94 | 159.2 | 159 |

⁹⁴ L. Malatesta and F. Turner, *Gazzetta*, 1942, **72**, 489.

⁹⁵ *Nature*, 1947, **160**, 502.

⁹⁶ *Ibid.*, 1948, **161**, 241.

⁹⁷ *Compt. rend.*, 1947, **224**, 124.

⁹⁸ D. I. Riabtschikov and E. A. Terentieva, *Compt. rend. Acad. Sci. U.R.S.S.*, 1946, **51**, 291.

⁹⁹ M. Fořx, *Compt. rend.*, 1946, **222**, 660.

¹ *Physical Rev.*, 1948, **74**, 773.

* The term actinon seems preferable to actinide. The justification for either lies in the elements 93—96 having the correct number of $5f$ -electrons for a series with its origin in actinium. The term does not presume the existence (as yet uncertain) of f -electrons in Th, Pa, or U, nor does it imply that those elements do not also show the valencies and properties of sub-groups IVA, VA, and VIA, respectively.

An article by A. G. Maddock,² with comprehensive bibliography, further reviews the chemistry of the actinons in the four radioactive series $4n$, $4n + 1$,³ $4n + 2$,⁴ $4n + 3$, and the growing evidence⁵ for regarding the actinons as a second series of f -shell elements.

W. H. Zachariasen⁷ has investigated the various two-component systems between sodium or potassium fluoride and UF_4 , ThF_4 , or LaF_3 and has tabulated lattice dimensions for KNb_2F_9 , KPu_2F_9 , NaPuF_5 , KPuF_5 , RbPuF_5 , and $\beta_2\text{-NaPuF}_4$. The analytical chemistry of thorium has been reviewed,⁸ as has the occurrence⁹ of uranium in minerals and its bearing on paragenesis, genetic history, and the geochemical cycle. Uranium oxides,^{10,11} UO , UO_2 , $\text{UO}_{2.34}$, U_3O_8 , and UO_3 , have been prepared and examined by X -rays, as have the carbides,^{11,12} UC , U_2C_3 , and UC_2 , and nitrides,¹¹ UN , U_2N_3 , and UN_2 . The oxide UO (only known from X -ray data), UC (action of methane on uranium above 625°), and UN have sodium chloride structures. U_2C_3 exists only at high temperatures ($>2000^\circ$); U_2N_3 is isomorphous with Mn_2O_3 and disproportionates with increased pressure to UN and UN_2 . UC_2 ($\text{U}_3\text{O}_8 + 14\text{C}$ or $\text{U} + 2\text{C}$ at 2400°) and UN_2 (stable only at high pressure) have CaC_2 structures. Preparation of uranium fluorides, UF_4 ,¹³ and U_2F_9 ,¹⁴ has been described. The latter is a black compound changing to green UF_4 on exposure to air and has a cubic structure where all the uranium atoms are equivalent. This indicates either that U(IV) , U(V) , and U(VI) replace each other isomorphously or that each uranium atom resonates between valency states of four and higher. A method of purification of UF_6 is described¹⁵ which enables it to be kept for long periods in previously well baked out vessels: vapour pressure, dielectric constant, and ultra-violet absorption have been measured. Uranium(IV) sulphate has been shown¹⁶ to be quantitatively coprecipitated with lanthanon sulphates

² *Research*, 1948, **1**, 690.

³ F. Hagemann, L. T. Katzin, M. H. Studier, A. Ghiorso, and G. T. Seaborg, *Physical Rev.*, 1947, **72**, 252; A. C. English, T. E. Cranshaw, P. Demers, J. A. Harvey, E. P. Hincks, J. W. Jelley, and A. N. May, *ibid.*, p. 253.

⁴ M. H. Studier and E. K. Hyde, *Physical Rev.*, 1948, **74**, 591.

⁵ C. A. Hutchinson and N. Elliott, *J. Chem. Physics*, 1948, **16**, 920.

⁷ *J. Amer. Chem. Soc.*, 1948, **70**, 2147.

⁸ T. Moeller, G. K. Schweitzer, and D. D. Starr, *Chem. Reviews*, 1948, **42**, 63.

⁹ S. I. Tomkief, *Sci. Progress*, 1946, **34**, 696.

¹⁰ F. Grönvold and H. Haroldson, *Nature*, 1948, **161**, 69; F. Grönvold, *ibid.*, 1947, **161**, 70; P. Jolibois, *Compt. rend.*, 1947, **224**, 1395.

¹¹ R. E. Rundle, N. C. Bamziger, A. S. Wilson, and R. A. McDonald, *J. Amer. Chem. Soc.*, 1948, **70**, 99.

¹² L. M. Litz, A. B. Garrett, and F. C. Croxton, *ibid.*, p. 1718.

¹³ H. S. Booth, W. Krasny-Ergen, and R. E. Heath, *ibid.*, 1946, **68**, 1969.

¹⁴ R. Livingston and W. Burns, Manhattan Project Report, CN 982, October, 1943; S. Weller, A. Grenall, and R. Kunin, Report A3326, March, 1945; W. H. Zachariasen, *J. Chem. Physics*, 1948, **16**, 425.

¹⁵ C. B. Amphlett, L. W. Mullinger, and L. F. Thomas, *Trans. Faraday Soc.*, 1948, **44**, 927.

¹⁶ A. W. Wylie, *Nature*, 1947, **160**, 830.

(under certain conditions), and hydrolysis of uranyl nitrate, both on dilution and with sodium hydroxide, has been followed¹⁷ potentiometrically. G. T. Seaborg and A. C. Wahl¹⁸ have given further chemical properties of neptunium and plutonium.

R. E. DODD.

P. L. ROBINSON.

¹⁷ H. Guiter, *Bull. Soc. chim.*, 1947, **14**, 64; 1946, **13**, 403.

¹⁸ *J. Amer. Chem. Soc.*, 1948, **70**, 1128.

ORGANIC CHEMISTRY.

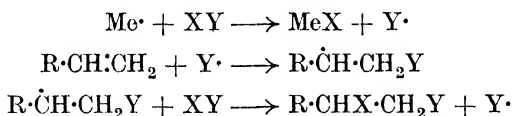
1. INTRODUCTION.

THE subjects selected for inclusion in this Report deal with some recently introduced general methods, developments in the reactions of free radicals and atoms, mono- and di-terpenes, colchicine and related compounds, some reactions of organic sulphur compounds, and certain groups of heterocyclic compounds.

In a survey of new general methods reference is made to the introduction of lithium aluminium hydride, which has proved to be a most useful reagent for effecting a wide variety of reductions, and in particular the ready conversion of $-\text{CO}_2\text{H}$ into $-\text{CH}_2\cdot\text{OH}$. The process of cyanoethylation is finding numerous applications in synthetic organic chemistry, and a considerable volume of new work has centred around the preparation and properties of cyanides. Particular reference should be made to the conversion of cyanides into amidines by a number of new reactions. The introduction of the $-\text{CH}_2\cdot\text{CO}_2\text{H}$ group directly into an aromatic nucleus has been effected by a dehydrogenating condensation with acetic anhydride and potassium permanganate. A general method for preparing amides has been reported which consists of heating the acid with urea. Several new general methods for the preparation of certain amino-acids have been published, and mention is made of the formation of a β -lactam from diazomethane and an isocyanate. Great advances have been made in the utilisation of simple compounds such as acetylene, ethylene, and carbon monoxide, and the processes of hydroxylation, chloromethylation, aminomethylation, sulphomethylation, nitrosation, oxynitration, and nitration (with sulphuric acid) have received considerable attention. Certain general reactions among organic compounds of phosphorus have now become firmly established. Dibenzyl chlorophosphonate has been employed in the synthesis of complex substances such as adenosine triphosphate, and esters of fluorophosphoric acid (having powerful anti-cholinesterase activity) are readily prepared by simple methods.

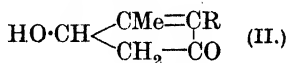
A survey of developments in the reactions of free radicals and atoms during the past four years shows that reactions of this type are more widespread than seemed likely a comparatively short time ago. Many new examples have been brought to light, and the added knowledge thus gained confirms and extends the main theoretical views which had already been developed. There is now clear evidence of a duality of function in many compounds which, under appropriate experimental conditions, can take part in either a homolytic or a heterolytic process. M. S. Kharasch and his collaborators have made an extensive study of the uses of acetyl peroxide, which acts as a convenient source of methyl radicals, and these investigations have led to the development of many novel synthetic methods.

The use of acyl peroxides for the alkylation of quinones has also been further extended. Considerable attention has been devoted to the kinetics of the decomposition of benzoyl peroxide in solvents; this is now considered to involve a secondary chain reaction in addition to the true unimolecular process. The remarkable properties of *tert.*-butyl peroxide have attracted wide interest; its reactions have been studied both in the vapour phase and in a variety of solvents, and a simple rate-determining dissociation process, involving the scission of the O-O bond, is common to both types of reaction. New contributions have been made to the theory of free-radical addition reactions, and a considerable extension of our knowledge of these reactions has resulted from further work on the addition to olefins under peroxidic conditions of various halogen derivatives of methane, derivatives of halogenated acids, phosphorus trichloride, trichlorosilane, and various sulphur compounds. These reactions can be represented by the general scheme :



The substitution reactions of atomic halogens have also been further explored. For bromination great use has been made of *N*-bromosuccinimide, and for chlorination further reactions have been described with sulphuryl chloride in the presence of a peroxide. New reactions which reveal a free-radical mechanism include those of diphenyliodonium hydroxide and phenyl iodosoacetate, and oxidation processes using selenium dioxide and chromic anhydride have also shown free-radical characteristics. The use of cobaltous chloride to induce free-radical reactions with Grignard reagents has been further extended.

The review of recent advances in the terpenes is limited to some aspects of the chemistry of the mono- and di-terpenes. The monoterpene section is devoted to the important series of esters derived from the chrysanthemum mono- and di-carboxylic acids (I; R = Me, and I; R = CO₂Me, respectively), monoterpene acids containing the unusual feature of an unfused *cyclo*-propane ring, and cyclic keto-alcohols of the type (II; R = alkyl or alkenyl). The esters derived from (II; R = CH₂·CH·CH·CHMe or CH₂·CH·CH·CH·CH₂) are the constituents of pyrethrum flowers (*Chrysanthemum cinerariifolium*) responsible for their remarkable insecticidal



properties. As these substances have not been reported on before, a brief survey has been made of the development of our knowledge of their structures from the time of their discovery by H. Staudinger and L. Ruzicka more than twenty-five years ago. Although their total synthesis has not yet been accomplished, the remaining difficulties should not prove insurmountable. By the study of synthetic analogues much light is being

thrown on the relationship of toxicity to structure. The section on the diterpenes is devoted to the resin acids containing the hydrophenanthrene skeleton. Although the structure of abietic acid was settled by 1941, the structures of sapietic, pimaric, and other resin acids have remained in doubt until recently. Conspicuous advances have been made in the isolation of primary resin acids, which have disclosed that abietic, dihydroabietic, and dehydroabietic acids, formerly regarded as artefacts, do in fact occur as such in pine oleoresin. The structure of pimaric acid has finally been settled as one containing a *gem*.-vinylmethyl group at C₇ in preference to a structure with an angular vinyl group at C₁₄. Work on agathic acid (a dicyclic diterpene) and on podocarpic acid, which is not a terpene although containing the hydrophenanthrene skeleton, is described, since this has an important bearing on the elucidation of the stereochemistry of the resin acids. The configurations of C₁, C₁₁, and C₁₂ have now been elucidated with reasonable certainty by a study of their interrelationships, by degradation to a common tricarboxylic acid in which ring A remains intact, and by a study of lactone formation in the dihydro-resin acids. The application of a theoretical analysis of the dissociation constants of the tricarboxylic acid to this configurational problem together with the suggestion that lactone formation is preceded by structural rearrangement (the angular methyl group migrating from C₁₂ to C₁₃) constitutes a useful additional approach to these problems.

The concept of *cycloheptatrienolone* (tropolone) as a new type of resonating aromatic system has proved extremely useful for interpreting the structures of a number of natural products. These are shown to range in complexity from the relatively simple mould-product stipitatic acid and a group of products isolated from the heartwoods of red cedar, through purpurogallin and its analogues which are now regarded as benzotropolone derivatives, to the tricyclic system of the acetylated alkaloidal amine, colchicine. In these compounds, generally, ethylenic and carbonyl functions are revealed by the results of hydrogenation but are masked towards the usual reagents and become incorporated in a carboxylated benzenoid ring through rearrangement in strongly alkaline media; there is supplementary evidence for the tropolone structure in most of them, and it now remains for the rational synthesis of a typical tropolone to set the seal on the degradative and interpretative work. The present state of the structural chemistry of colchicine is reviewed. Recent work indicates that the compound may contain a second 7-membered ring in addition to the tropolone system. After the tropolone ring has been converted into a benzenoid form, further degradation yields products which are identified as dibenz-*cycloheptatrienes*. Attention is thereby directed to the synthesis and transformations of compounds of this type.

In recent years, interest in the chemistry of organic sulphur compounds has been stimulated by the discovery of several physiologically active natural products containing sulphur—for example, aneurin, biotin, and penicillin. At the same time, an appreciation of the use of organic sulphur

compounds, which are often more reactive than their oxygen analogues, has led to new synthetic methods and improvements on previously known ones. In 1939 the remarkable discovery was made that sulphur can be removed from, or replaced by, hydrogen in many different types of inorganic and organic substance by means of Raney nickel. This reaction has already found numerous applications in synthetic work, and has been particularly useful for the elucidation of the structure of organic sulphur compounds : thus it was of great importance in connection with biotin and penicillin. Raney-nickel hydrogenolysis does not cause racemisation of optically active molecules ; for example, natural(—)methionine yields L(+)- α -aminobutyric acid, thereby confirming that the former has the same absolute configuration as the other natural (L) α -amino-acids. Similarly, the stereochemistry of penicillin and of the natural and synthetic stereoisomers of biotin has been studied. The ease of cyclisation of many thioacylamido-compounds has led to new methods for the synthesis of derivatives of glyoxaline, oxazole, and thiazole. The required intermediates can sometimes be made by the action of phosphorus pentasulphide on the corresponding amides, but this reaction is not always satisfactory. A much better method is the direct thioacylation of amines by means of dithioacids, their salts or esters, or by thion-esters. The Willgerodt and Kindler reactions have been studied extensively in the last few years and so modified that excellent yields of substituted phenylacetic acids are now obtainable. The preparation of aromatic aldehydes by the McFadyen-Stevens and the Wuyts reaction, the use of thiourea for the synthesis of pyrimidines and purines, of 5-methylthiuronium salts for guanidines and rhodanine, and of 2-thiothiazoline for α -amino-acids have also been outlined.

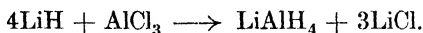
In the heterocyclic series the chemistry of aziridines, β -biotin, and the pterins is reviewed. Under the first heading attention is directed to the more recent interest shown, since 1941, in the preparation and properties of ethyleneimines. Under the second heading recent syntheses of three of the stereoisomeric racemates of the biotin structure including the hitherto unknown (\pm)-*epibiotin* are outlined. By chemical control of configurations the methods make feasible the preparation of all four racemates from a single intermediate, and the need to separate mixtures of racemates is thereby obviated. Finally, a review is included of the advances made in the field of pterin chemistry since the previous Report of two years ago. New syntheses of vitamin B₆ and pteric acid are reported together with experiments concerning the degradation and synthesis of the fermentation *L. casei* factor and a new pterin growth-factor, rhizopterin. Attention is directed to investigations on the reduction of some pteridines, including vitamin B₆, the synthesis of compounds antagonistic to vitamin B₆, and preparations of numerous simpler pteridines. Experiments on the utilisation of sugars, and recent views concerning the authenticity of preparations of hydroxy- or halogeno-methylpteridines, are also reported.

D. H. H.
B. J.

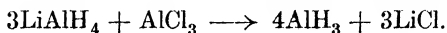
2. GENERAL METHODS.

Reduction.—Since the last Report on General Methods,¹ outstanding advances have centred round the use of lithium aluminium hydride, LiAlH_4 . The organic chemist has always been handicapped by the lack of a suitable general method for converting the $-\text{CO}_2\text{H}$ group into $-\text{CH}_2\cdot\text{OH}$. This new reagent now promises to give the answer to this age-long problem, and to be of considerable general use in effecting a wide variety of reductions.

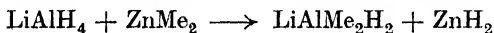
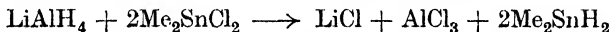
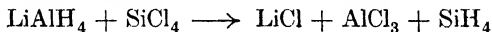
Lithium aluminium hydride was discovered in 1947 by A. E. Finholt, A. C. Bond, and H. I. Schlesinger² who treated finely divided lithium hydride with an ethereal solution of aluminium chloride. Lithium aluminium hydride was thus obtained as an ether-soluble solid according to the equation :



Larger quantities of aluminium chloride gave aluminium hydride :



By the use of lithium aluminium hydride, new methods, simpler than those already available, were at once developed for the preparation of hydrides such as silane and stannane and of their alkylated derivatives. (The hitherto unknown hydrides of zinc and beryllium have also been prepared.) :



These reactions usually proceed smoothly at room temperature, and give high yields of pure products. The authors point out that in certain reductions of this type lithium hydride and aluminium hydride can be used in place of lithium aluminium hydride. With lithium hydride, however, the reactions are slower and the yields poorer.

R. F. Nystrom and W. G. Brown³ used lithium aluminium hydride for reducing aldehydes, ketones, esters, and acid chlorides to the corresponding alcohols. The reaction proceeds in ether, at room temperature, and yields are of the order 70—98%. Points in favour of this reagent are : (a) no special apparatus is required, (b) it is claimed to be indefinitely stable at room temperature. The most notable advance, however, by these authors, concerns the smooth reduction of carboxylic acids⁴ to the corresponding primary alcohol by lithium aluminium hydride. An ethereal solution of the acid is added dropwise to an ethereal solution of the reagent at such a rate as to maintain a gentle reflux. After 15 minutes, the cooled product is diluted with water and treated with 10% sulphuric acid (or 10% sodium hydroxide solution), leaving the alcohol in the ethereal layer. Free hydroxyl and amino-groups do not interfere. The double bond in cinnamic acid, but not those in sorbic or furoic acid, is simultaneously hydrogenated.

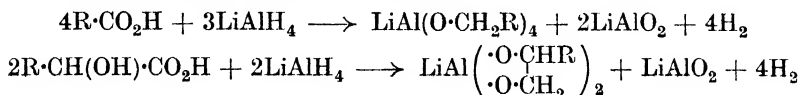
¹ R. A. Baxter and F. S. Spring, *Ann. Reports*, 1945, **42**, 96.

² *J. Amer. Chem. Soc.*, 1947, **69**, 1199.

³ *Ibid.*, p. 1197.

⁴ *Ibid.*, p. 2548.

It is possible that the equations for the reduction of simple monocarboxylic acids and hydroxy-acids are as follows, although there is little direct experimental evidence in support of these :



A few experimental results are summarised in the Table.

| Acid. | Product. | Yield (%). |
|----------------------|-------------------------------|------------|
| Trimethylacetic acid | <i>neo</i> Pentyl alcohol | 92 |
| Stearic acid | Octadecanol | 91 |
| Sebacic acid | Decane-1 : 2-diol | 97 |
| Phenylacetic acid | 2-Phenylethanol | 92 |
| Cinnamic acid | 3-Phenylpropyl alcohol | 85 |
| Benzoic acid | Benzyl alcohol | 81 |
| Anthranilic acid | <i>o</i> -Aminobenzyl alcohol | 97 |
| Phenyglyoxylic acid | Phenylethylene glycol | 80 |

From the experimental data so far available it appears to be a characteristic of the reagent that ethylenic linkages, substituted on one side by a phenyl group and on the other by a reducible group (*e.g.*, carboxyl, carbonyl, nitro-, etc.) are hydrogenated. Other ethylenic linkages do not appear to be attacked: crotonaldehyde, for example, gives crotyl alcohol, hence the value of the reagent in preparing certain types of unsaturated alcohols.

Further evidence⁵ of the versatility of lithium aluminium hydride is shown by its ability to reduce carbon dioxide to methanol in 81% yield.

G. Darzens⁶ has shown that sodium hydride (NaH) can replace sodium in the Bouveault-Blanc method of reducing esters to alcohols, with improved yields. Glycerides of aliphatic acids as well as aldehydes and ketones can be reduced in the same way. It may well be that sodium hydride is in fact the actual reducing agent in the standard Bouveault-Blanc reaction, although V. L. Hansley⁷ expresses a different view. Darzens also claims that calcium hydride does not cause reduction under the same conditions.

Some interesting results have been obtained by G. H. Hargreaves and L. N. Owen⁸ who give examples of the reduction of aliphatic ketones by simple primary aliphatic alcohols in the presence of concentrated aqueous alkali at 240°.

Considerable attention is still being paid to the partial hydrogenation of the acetylenic linkage. W. E. Baker and D. J. Kennedy⁹ give details for the utilisation of cathodically formed chromous chloride for the reduction of acetylene to ethylene in 95% yield. It appears that the reduction can also be carried out¹⁰ by passing a mixture of acetylene, hydrogen, and

⁵ R. F. Nystrom and W. H. Yanko, *J. Amer. Chem. Soc.*, 1948, **70**, 441.

⁶ *Compt. rend.*, 1947, **224**, 570.

⁷ *Ing. Eng. Chem.*, 1947, **39**, 55.

⁸ *J.*, 1947, 750, 753.

⁹ *Trans. Electrochem. Soc.*, 1947, **92**, 231.

¹⁰ H. Ohe, *J. Soc. Chem. Ind. Japan*, 1946, **49**, 165.

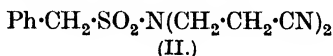
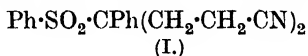
steam at atmospheric pressure through a catalyst consisting of a 1 : 10 mixture of nickel and kieselguhr at 110—200°; a yield of 60% is claimed. What might prove to be a very important reaction, if technical development is possible, is the hydrogenation of vinylacetylene at ordinary temperatures with Raney nickel, nickel-aluminium oxide, palladium-barium sulphate, or chromous chloride as catalysts.¹¹ Butadiene is obtained as the sole product in yields of 75—78%. This partial reduction can also be carried out by electrolysing the weakly alkaline solution (platinum and platinised platinum electrodes).

Titanium hydride may perhaps prove of some use as a catalyst for the selective hydrogenation of the $\text{-C}\equiv\text{C-}$, $\text{-C}\equiv\text{N}$ and $\text{N}=\text{O}$ groups.¹²

J. E. Dubois has shown¹³ that Raney nickel in the absence of molecular hydrogen can promote the exchange of hydrogen through simultaneous dehydrogenation and hydrogenation reactions. Thus keto-alcohols yield diketones and diols. Experiments show that the hydrogenation is not due to hydrogen occluded in the nickel. It is interesting to note that when certain substituted formamides are heated in the presence of Raney nickel at 190°, aldehydes and ketones¹⁴ are formed thus: $\text{H}\cdot\text{CO}\cdot\text{NH}\cdot\text{CHRR}' \longrightarrow \text{R}\cdot\text{COR}'$. The reaction occurs if the α -carbon atom of the formamide is mono- or di-substituted. Trisubstitution results in the regeneration of the parent amine. As an extension of this general reaction, it is claimed that acetanilide gives cyclohexanone.

E. C. Kleiderer and E. C. Kornfield¹⁵ have used Raney nickel in the presence of a hydrogen acceptor (*e.g.*, cyclohexanone) to oxidise secondary alcohols to ketones. The reaction was carried out simply by boiling under reflux for 24 hours. They also used the process in the reverse sense, *i.e.*, as a reductive method in the presence of a hydrogen donor (*e.g.*, cyclohexanol): this reaction constitutes an extension of the work of Mozingo *et al.*¹⁶

Cyanoethylation.—The utilisation of the process of cyanoethylation goes on apace, and vinyl cyanide (acrylonitrile) is now a compound of extremely varied and useful application in synthetic organic chemistry. Since the last Report¹⁷ on this topic mention may be made of the addition of vinyl cyanide to aryl sulphones¹⁸ in the presence of benzyltrimethylammonium hydroxide as a catalyst. Thus phenyl benzyl sulphone gives (I).



A recent investigation¹⁹ of the reaction between vinyl cyanide and toluene- ω -sulphonamide $\text{Ph}\cdot\text{CH}_2\cdot\text{SO}_2\cdot\text{NH}_2$ proves that two cyanoethyl groups

¹¹ A. L. Klebansky, L. D. Popov, and N. Ya Tsukerman, *J. Gen. Chem. Russia*, 1946, **16**, 2083.

¹² U.S.P. 2,418,441.

¹³ *Compt. rend.*, 1947, **224**, 1234.

¹⁴ M. Metayer, *ibid.*, 1948, **226**, 500.

¹⁵ *J. Org. Chem.*, 1948, **13**, 455.

¹⁶ R. Mozingo, C. Spencer, and K. Folkers, *J. Amer. Chem. Soc.*, 1944, **66**, 1859.

¹⁷ F. S. Spring, *Ann. Reports*, 1943, **40**, 108.

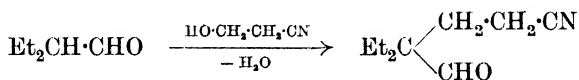
¹⁸ H. A. Bruson, U.S.P. 2,435,552.

¹⁹ H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, 1948, **70**, 214.

become attached to the nitrogen giving *NN*-di-(2-cyanoethyl)benzylsulphonamide (II). (Earlier work ²⁰ had indicated that the cyanoethyl groups were attached to the methylene carbon atom.) Hydrolysis of (II) gives β -(benzylsulphonamido)propionic acid, $\text{Ph}\cdot\text{CH}_2\cdot\text{SO}_2\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.

In the presence of alkaline condensing agents, one or two molecules of an aldehyde $\text{CHRR}'\cdot\text{CHO}$ will condense with vinyl cyanide.²¹ Thus acetaldehyde gives γ -cyanobutaldehyde $\text{CN}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHO}$ and di-(2-cyanoethyl)acetaldehyde (γ -formylpimelonitrile), $(\text{CN}\cdot\text{CH}_2\cdot\text{CH}_2)_2\text{CH}\cdot\text{CHO}$.

Cyanoethylation without using vinyl cyanide has been effected by H. A. Bruson and W. D. Niederhauser.²² According to this method, aldehydes and ketones having a reactive hydrogen are heated with ethylene cyanohydrin at 82–100° with an alkaline catalyst and in a solvent which removes water on distillation.



2-Chloroethyl cyanide is obtained in high yield by the addition of 0.95 equivalent of dry hydrogen chloride at 0° to vinyl cyanide.²³ A new method ²⁴ for preparing $\alpha\beta$ -dichloropropionic acid consists in passing chlorine into a suspension of vinyl cyanide in 36% hydrochloric acid at 50–60°. When the requisite amount of chlorine has been absorbed the mixture is refluxed to complete the hydrolysis. Starting with 1-methylallyl cyanide, dichloroisobutyric acid can be prepared. The dibromo-acids are obtainable in a similar way.

Succinic acid is readily obtainable as a result of the cyanoethylation of hydrogen cyanide in the presence of an alkaline condensing agent (*e.g.*, quaternary ammonium hydroxides, aliphatic amines, or inorganic cyanides) which gives ethylene cyanide ²⁵: $\text{HCN} + \text{CH}_2\cdot\text{CH}\cdot\text{CN} = \text{CN}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$.

Details for the laboratory preparation of 2-cyanoethylamine and di-(2-cyanoethyl)amine in 33% and 57% yield respectively from vinyl cyanide and aqueous ammonia have been given.²⁶ [Higher yields of the primary amine (up to 80%) have been obtained by adding vinyl cyanide to preheated ammonia in a steel autoclave.] By the use of barium hydroxide 2-cyanoethylamine is readily hydrolysed ²⁷ to β -alanine, $\text{NH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$; this appears to constitute the best method so far recorded of preparing this amino-acid.

Attempts have been made to develop a new synthesis ²⁸ of derivatives of chroman by the cyanoethylation of the hydroxyl group of salicylaldehyde followed by an aldol cyclisation in a single-stage process. So far only very small yields have been obtained in this way. A successful preparation of a

²⁰ Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 25.

²¹ B.P. 576,427.

²² U.S.P. 2,437,906.

²³ R. Stewart and R. H. Clark, *J. Amer. Chem. Soc.*, 1947, **69**, 713.

²⁴ U.S.P. 2,365,808.

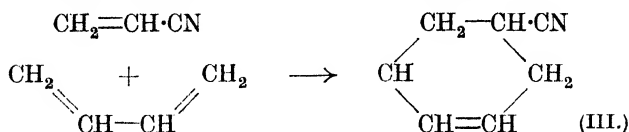
²⁵ U.S.P. 2,434,606.

²⁶ *Org. Synth.*, 1947, **27**, 3.

²⁷ *Ibid.*, p. 1.

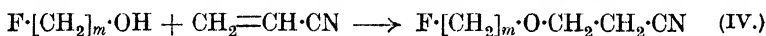
²⁸ G. B. Bachmann and H. A. Levine, *J. Amer. Chem. Soc.*, 1948, **70**, 599.

cyclic compound²⁹ has been made by the addition of vinyl cyanide to butadiene in toluene solution, in the presence of quinol in a sealed tube; 1-cyanocyclohex-3-ene (III) is thus obtained in 80% yield.



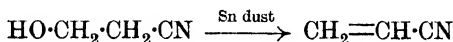
F. G. Mann and R. C. Cookson³⁰ have found that phenylarsine and two molecular proportions of vinyl cyanide readily give the crystalline phenyldi-(2-cyanoethyl)arsine, $\text{Ph}\cdot\text{As}(\text{CH}_2\cdot\text{CH}_2\cdot\text{CN})_2$. This cyano-arsine was found to be useful as an intermediate in the preparation of a new type of arsine-amidine, $\text{Ph}\cdot\text{As}[\text{CH}_2\cdot\text{CH}_2\cdot(\text{C}^+\text{NH}_2)\cdot\text{NH}_2, \text{N}\bar{\text{O}}_3]_2$.

A novel application of the process of cyanoethylation has been employed by B. C. Saunders³¹ in the preparation of long-chain ω -fluoro-carboxylic acids having a hetero-oxygen atom in any desired position. These acids, of the general formula $\text{F}\cdot[\text{CH}_2]_m\cdot\text{O}\cdot[\text{CH}_2]_n\cdot\text{CO}_2\text{H}$, are used for pharmacological work in connection with β -oxidation processes, and are prepared as follows :



The compound (IV) was then lengthened at the cyanide end, either by reduction of the $-\text{CN}$ to $-\text{CH}_2\cdot\text{NH}_2$ followed by standard procedures, or by hydrolysis to the acid followed by Arndt-Eistert reactions.

Numerous patents cover the preparation of vinyl cyanide in high yield by the catalytic addition of hydrogen cyanide to acetylene.³² Russian workers have devised a process which avoids the use of hydrogen cyanide.³³ Ethylene oxide is passed into a saturated solution of potassium cyanide and magnesium sulphate at 0° , and the ethylene cyanohydrin thus produced is dehydrated by means of tin dust :



Substituted vinyl cyanides³⁴ of the general formula $\text{CH}_2=\text{CR}\cdot\text{CN}$ are conveniently made by the reaction of a cyanide, $\text{R}\cdot\text{CH}_2\cdot\text{CN}$ (where $\text{R} = \text{H}$, alkyl or aryl), with formaldehyde in the vapour phase over a dehydration catalyst.

Cyanides (other than Vinyl Cyanide).—Useful information regarding the preparation of cyanides is given in an article by D. T. Mowry.³⁵ The simplest hydroxy-cyanide, $\text{CH}_2(\text{OH})\cdot\text{CN}$, is easily prepared in 80% yield by action of potassium cyanide on aqueous formaldehyde.³⁶

²⁹ A. A. Petrov and N. P. Sopor, *J. Gen. Chem. Russia*, 1947, **17**, 2228.

³⁰ *Nature*, 1946, **157**, 846; *J.*, 1947, 618.

³¹ *Nature*, 1947, **160**, 179.

³² This list is not exhaustive, but the following are representative: U.S.P. 2,407,124; 2,385,561; 2,413,476; 2,413,623; 2,419,186. B.P. 581,035; 593,851.

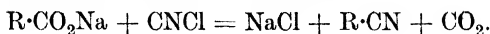
³³ A. P. Terentiev and E. Y. Vinogradova, *J. Gen. Chem. Russia*, 1944, **14**, 1046.

³⁴ U.S.P. 2,386,586.

³⁵ *Chem. Reviews*, 1948, **42**, 189.

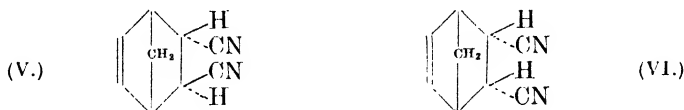
³⁶ R. Gaudry, *Org. Synth.*, 1947, **27**, 41.

A new general method of converting an acid (or better, its alkali salt) directly into the nitrile in one stage ³⁷ depends upon treatment with cyanogen chloride at 200—300° according to the equation :



The reaction does not depend upon the nature of R, except in so far as the acid or its sodium salt must withstand the temperature quoted.

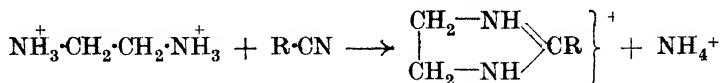
It is well established that the cyano-group confers considerable dienophilic activation upon a double bond in the 1:2-position. It is therefore not surprising to learn that *trans*- and *cis*-1:2-dicyanoethylene (fumaronitrile and maleonitrile) react with extreme ease ³⁸ with cyclopentadiene forming the corresponding cyanides (V) and (VI). Mowry ³⁹ has shown that the reaction with *trans*-1:2-dicyanoethylene is of very wide application.



A rather unexpected reaction is that between benzyl cyanide and formamide, the main product being 4-amino-5-phenylpyrimidine ⁴⁰ (VIII). The mechanism of this reaction would seem to involve the direct condensation of benzyl cyanide with formamide giving iminomethylbenzyl cyanide (VII) which on further reaction with formamide followed by cyclisation gives (VIII).



Amidines [$R \cdot C(\text{NH}) \cdot \text{NH}_2$] and their *N*-monosubstituted derivatives can conveniently be prepared ⁴¹ by heating the ammonium or alkylammonium salt of an aliphatic or aromatic sulphonic acid with an organic cyanide at 180—300°. Somewhat higher yields appear to be possible if the cyanide is heated with ammonium or a substituted ammonium thiocyanate. ⁴² The method has been successfully extended to the synthesis of substituted dihydroglyoxalines and ring homologues ⁴³ by the reaction :



Unless a cyanide contains a polar group which can stimulate the additive capacity of the cyano-group, direct addition with ammonia or amines does not take place. Catalysts, however, of the Friedel-Crafts type enhance the

³⁷ E. V. Zappi and O. Bonso, *Anal. Asoc. Quím. Argentina*, 1947, **35**, 137.

³⁸ A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, 1945, **10**, 149.

³⁹ *J. Amer. Chem. Soc.*, 1947, **69**, 573.

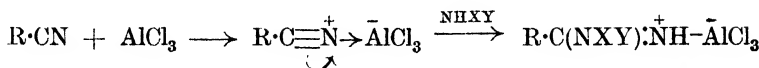
⁴⁰ W. D. Davies and W. A. Piggott, *J.*, 1945, 347.

⁴¹ P. Oxley and W. F. Short, *J.*, 1946, 147.

⁴² M. W. Partridge and W. F. Short, *J.*, 1947, 390.

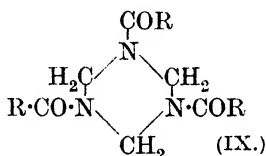
⁴³ P. Oxley and W. F. Short, *J.*, 1947, 497.

dipole condition of the cyanide and so increase its reactivity toward ammonia and amines :



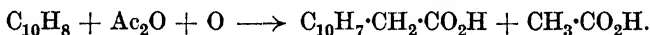
This observation forms the basis of yet another new method⁴⁴ for preparing amidines and *N*-substituted amidines.

An entirely new general reaction of cyanides has been recorded by M. A. Gradsten and M. W. Pollock.⁴⁵ They have shown that formaldehyde (as trioxymethylene) will react with alkyl, aryl, unsaturated, and halogen-substituted cyanides, in the presence of sulphuric acid as catalyst, giving hexahydro-*s*-triazines of the general formula (IX). This structure appears to be fully confirmed by infra-red evidence.



A very useful stepwise reduction of dicyanides has been observed.⁴⁶ Thus $\text{CN}\cdot[\text{CH}_2]_n\cdot\text{CN}$ in *n*-butanol with Raney nickel and hydrogen at 75–80° and ordinary pressures gives $\text{CN}\cdot[\text{CH}_2]_{n+1}\cdot\text{NH}_2$. An easy method of preparing ω -amino-acids here presents itself. In an autoclave at 110° and 90 atm. the reduction product is $\text{NH}_2\cdot[\text{CH}_2]_{n+2}\cdot\text{NH}_2$.

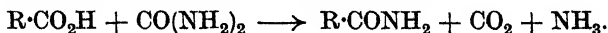
Acids and their Derivatives.—A new and remarkable method for preparing naphthalene-1-acetic acid consists in boiling a mixture of naphthalene, acetic anhydride, and potassium permanganate for 20 minutes.⁴⁷ The overall reaction appears to be a dehydrogenating condensation.



The reaction is not limited to naphthalene; anisole, for example, gives *p*-methoxyphenylacetic acid.

A new method of esterification⁴⁸ consists in treating a dry sodium salt, $\text{R}\cdot\text{CO}_2\text{Na}$, with $\text{Cl}\cdot\text{SO}\cdot\text{OR}'$ and heating the $\text{R}\cdot\text{CO}_2\text{SO}\cdot\text{OR}'$ first formed to give $\text{R}\cdot\text{CO}_2\text{R}'$. The method appears to be general for primary alkyl chlorosulphites and applicable to aliphatic, aromatic, and certain sterically hindered acids.

A new general method for preparing amides⁴⁹ in good yield consists in heating an acid with urea (reaction begins at 120°) :



⁴⁴ P. Oxley and W. F. Short, *J.*, 1947, 1110.

⁴⁵ *J. Amer. Chem. Soc.*, 1948, 70, 3079.

⁴⁶ B. A. Arbuzov and E. A. Pozhiltzova, *Bull. Acad. Sci. U.R.S.S., Classe Sci. Chim.*, 1946, 65.

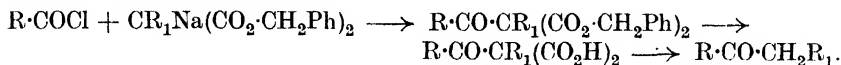
⁴⁷ W. Griehl, *Chem. Ber.*, 1947, 80, 410.

⁴⁸ M. S. Newman and W. S. Fones, *J. Amer. Chem. Soc.*, 1947, 69, 1046.

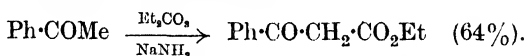
⁴⁹ E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, 1946, 29, 1438.

Thus acetic acid gives 95% of acetamide, and nicotinic acid gives 85% of nicotinamide. Sulphuric acid gives $\text{HO}\cdot\text{SO}_2\cdot\text{NH}_2$ then $\text{SO}_2(\text{NH}_2)_2$. Substituted ureas behave similarly; thus nicotindiethylamide is obtained from nicotinic acid and $\text{CO}(\text{NHEt})_2$ at 220—280°.

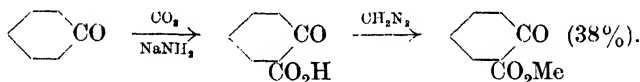
Benzyl esters of acylmalonic acids readily undergo hydrogenolysis at room temperature in the presence of palladised charcoal with formation of acids which on being warmed (50—70°) lose 2 mols. of carbon dioxide and give ketones in excellent yields : ⁵⁰



Many β -keto-esters are conveniently synthesised by the action of ethyl carbonate on the sodium derivative of a ketone ⁵¹ (prepared by the action of sodamide and liquid ammonia on the ketone). An excess of sodamide is efficacious in effecting the condensation :

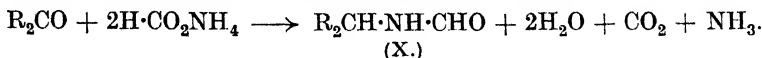


Treatment of the sodium derivative of a ketone with solid carbon dioxide, followed by the action of diazomethane, gives the methyl ester of a β -keto-acid.



Acylation.—A variety of aromatic hydrocarbons can be acetylated simply by being boiled under reflux with glacial acetic acid and phosphoric oxide. ⁵² Thiophen can be directly acylated ⁵³ by means of $\text{R}\cdot\text{CO}_2\text{H}$ and phosphoric oxide in an inert solvent. Furan is similarly acylated, but in lower yield. Boron trifluoride catalyses the interaction in nitrobenzene of benzoic anhydride with aromatic compounds to give ketones. ⁵⁴ In this way thiophen gives a 40% yield of phenyl 2-thienyl ketone.

Amines.—In 1885 R. Leuckart ⁵⁵ first described the conversion of certain aldehydes and ketones into amines by heating with excess of ammonium formate. This reaction has recently received a great deal of attention and good yields can be obtained, ⁵⁶ but the mechanism is still not understood. Superficially the primary reaction is :



⁵⁰ R. E. Bowman, *Nature*, 1948, **162**, 111.

⁵¹ R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1768; see also H. G. Walker, R. Levine, R. F. Kibler, and C. R. Hauser, *ibid.*, 1946, **68**, 672.

⁵² G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1947, **69**, 1651.

⁵³ H. D. Hartough and A. I. Kosak, *ibid.*, p. 3098.

⁵⁴ P. H. Given and D. Ll. Hammick, *J.*, 1947, 1237.

⁵⁵ *Ber.*, 1885, **18**, 2341.

⁵⁶ F. S. Crossley and M. L. Moore, *J. Org. Chem.*, 1944, **9**, 529; L. H. Goodson, C. J. W. Wiegand, and J. S. Splitter, *J. Amer. Chem. Soc.*, 1946, **68**, 2174; A. W. Ingersoll *et al.*, *ibid.*, 1936, **58**, 1810; see also *Org. Synth.*, **2**, 503.

It is now usual to hydrolyse the formyl derivative (X) with concentrated hydrochloric acid. Although formamide can replace ammonium formate (giving, however, smaller yields), it now appears established that ammonium formate is both necessary and sufficient for the reaction.⁵⁷ Benzylamine is readily obtained by the hydrolysis of $\text{Ph}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{COMe}$, obtained by heating benzyl chloride with acetamide at 200° for 8 hours.⁵⁸

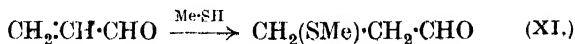
Solid aryldiazonium sulphates are obtainable from all amines capable of diazotisation.⁵⁹ The amine in cold acetic acid is treated with sodium nitrite in sulphuric acid at 0° , and the diazonium salt is precipitated by ether. The method for converting a diazonium salt into a nitro-compound⁶⁰ has been extended to naphthylamines, benzidine, and 3 : 3'-dinitrobenzidine, as follows : the solid diazonium sulphate (or its aqueous solution) is added to a saturated solution of sodium nitrite containing cupro-cupri sulphite (prepared by adding aqueous sodium sulphite to copper sulphate and stirring the precipitate into saturated sodium nitrite).

N. I. Sheverdina and K. A. Kocheshkov⁶¹ showed in 1938 that *O*-methylhydroxylamine would react with a Grignard compound as follows :



The product on treatment with hydrochloric acid gave the amine hydrochloride, $\text{R}\cdot\text{NH}_3\text{Cl}$. R. Brown and W. E. Jones⁶² have recently improved the conditions of the reaction and have shown that the product is uncontaminated by the corresponding secondary and tertiary compounds. The reaction is also applicable to certain dibromides such as pentamethylene dibromide which gives cadaverine in 68% yield.

Amino-acids.—Hitherto no satisfactory method has existed for the synthesis of DL-methionine and related amino-acids. The catalysed addition of methylthiol to commercial acraldehyde to give β -methylthiopropaldehyde (XI) in high yield has now provided the basis of excellent methods for synthesising a variety of sulphur-containing amino-acids of the methionine type in good overall yield :



J. R. Catch, A. H. Cook, A. R. Graham, and (Sir) I. M. Heilbron⁶³ have converted (XI) into the cyanohydrin and thence into the corresponding

⁵⁷ E. R. Alexander and R. B. Wildman, *J. Amer. Chem. Soc.*, 1948, **70**, 1187.

⁵⁸ M. A. Phillips, *J. Soc. Chem. Ind.*, 1947, **66**, 325.

⁵⁹ H. H. Hodgson and J. Walker, *J.*, 1933, 1620; H. H. Hodgson and A. P. Mahadevan, *J.*, 1947, 325.

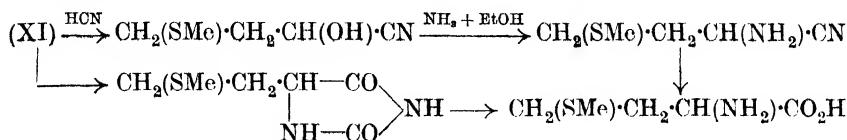
⁶⁰ H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, *ibid.*, p. 1392; see also H. H. Hodgson, F. Heyworth, and E. R. Ward, *J.*, 1948, 1572.

⁶¹ *J. Gen. Chem. Russia*, 1938, **8**, 1825.

⁶² *J.*, 1946, 781; for preparation of *O*-methylhydroxylamine, see W. Traube, H. Ohlendorf, and H. Zauder, *Ber.*, 1920, **53**, 1477.

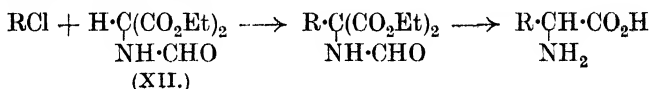
⁶³ *Nature*, 1947, **159**, 578; *J.*, 1947, 1609.

amino-cyanide (isolated as oxalate) which was hydrolysed to methionine (29% yield based on acraldehyde).



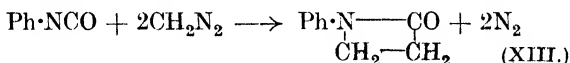
E. Pierson, M. Giella, and M. Tischler⁶⁴ have used this method with slight modification of practical details and have also successfully employed the Bücherer hydantoin reaction followed by hydrolysis. The yield of methionine (from acraldehyde) based on this alternative method was 50%.

A. Gelat⁶⁵ has found ethyl formamidomalonate (XII) (from ethyl malonate, sodium nitrite, and acetic acid followed by reduction with zinc and formic acid) to be a useful intermediate in the synthesis of amino-acids. (XII) is condensed with benzyl chloride or ethyl chloroacetate, and the products (without isolation) are hydrolysed giving DL-phenylalanine and DL-aspartic acid respectively :



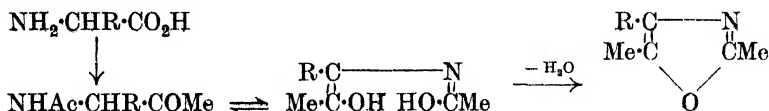
Condensation of (XII) with vinyl cyanide followed by hydrolysis gives DL-glutamic acid. Earlier work along these lines was carried out by N. F. Albertson and S. Archer,⁶⁶ and by H. D. Dakin.⁶⁷

A novel synthesis of a β -lactam has recently been reported.⁶⁸ Phenyl isocyanate and diazomethane react in ethereal solution as follows :



If the reaction proves to be general, it might be of considerable use in synthetic studies. Hydrolysis with sodium hydroxide followed by acidification converted (XIII) into *N*-phenyl- β -alanine.

A method for converting α -amino-acids into oxazoles has been developed.⁶⁹ Alanine, for example, gives 3-acetamidobutan-2-one by treatment with acetic anhydride and pyridine. The ketone is then converted into 2:4:5-trimethyloxazole. It is possible that the course of these reactions is as follows :



⁶⁴ *J. Amer. Chem. Soc.*, 1948, **70**, 1450.

⁶⁵ *Ibid.*, 1947, **69**, 965.

⁶⁶ *Ibid.*, 1945, **67**, 308.

⁶⁷ *J. Biol. Chem.*, 1943, **154**, 553.

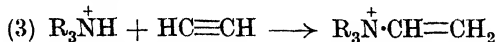
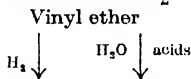
⁶⁸ J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, 1948, **70**, 1985.

⁶⁹ R. H. Wiley, *J. Org. Chem.*, 1947, **12**, 43; cf. also R. Robinson *et al.*, *J.*, 1909, 2167; 1912, 1297.

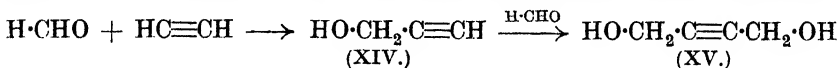
A useful technique for separating strong acids from their aqueous solutions containing weak acids including amino-acids has been developed ⁷⁰ depending upon the acid-binding properties of long-chain aliphatic amines [e.g., methyldioctylamine (in chloroform or nitrobenzene)]. Efficiency improves with the length of the chain and in the order tertiary > secondary > primary. The method has been applied successfully to the removal of mineral acids from protein hydrolysates, but does not appear to be of much value for extraction or purification of penicillin. Among the possible applications of this extraction technique is the removal of mineral acid used in the hydrolysis of a polysaccharide.

It is not easy to prepare water-soluble amino-acids from their alkali-metal salts, since treatment with acids yields mixtures, the components of which have similar solubilities. A. Gelat ⁷¹ found that very satisfactory results are, however, obtained by the use of ethyl oximinocynoacetate. ⁷² The ester, used in alcohol, is sufficiently acidic to liberate amino-acids from their salts (in aqueous solution). The alkali-metal salts are soluble in the aqueous alcohol whereas the amino-acid separates if appropriate condition are used.

Acetylenic Compounds.—A vast amount of work has been carried out on acetylenic compounds during recent years, and in this Report attention is drawn only to certain reactions which are likely to be of general application. Reference should be made to German work by J. W. Reppe and his colleagues, and to two recent books by A. W. Johnson and E. D. Bergmann. ⁷³ In the first of these references a description is given of the process of "vinylation," i.e., the addition of an alcohol, phenol, thiol, carboxylic acid, primary or secondary amine, amide, or trialkylammonium radical to acetylene in the presence of an alkaline catalyst. The following equations serve to indicate the importance of some of these reactions :



"Ethynylation" is readily brought about by allowing an aldehyde or ketone to react with acetylene in the presence of cuprous acetylide as catalyst :



⁷⁰ E. L. Smith and J. E. Page, *J. Soc. Chem. Ind.*, 1948, **67**, 48.

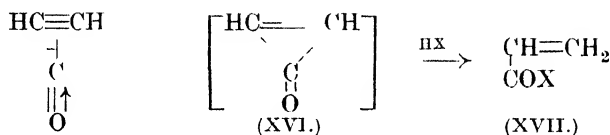
⁷¹ *J. Amer. Chem. Soc.*, 1947, **69**, 707.

⁷² N. Conrad and A. Schultze, *Ber.*, 1909, **42**, 735.

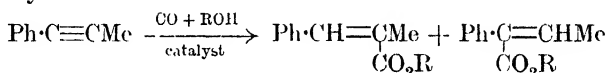
⁷³ "The chemistry of some new technical applications of acetylene," BIOS, Item 22, Stationery Office, London; A. W. Johnson, "Acetylenic Compounds," Vol. I., Edward Arnold & Co.; E. D. Bergmann, "Chemistry of Acetylene and Related Compounds," Interscience Publishers.

The butynediol (XV) can be converted by hydrogenation into butanediol which on dehydration gives butadiene. On hydrogenation, propargyl alcohol (XIV) gives allyl alcohol and then *n*-propanol, depending upon the nature of the catalyst and pH.

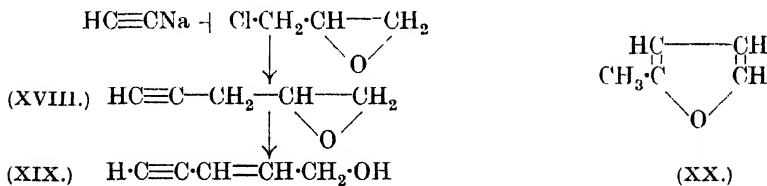
"Carbonylation" takes place when acetylene reacts with carbon monoxide and a compound of the type HX (X = OH, OR, SR, NHR, etc.) in the presence of nickel carbonyl as catalyst. It has been suggested that the hypothetical cyclopropenone (XVI)* is first formed, and that this reacts with HX giving acrylic acid (XVII) or one of its derivatives. The yield is almost quantitative:



The reaction appears to be general, since acetylene can be replaced by substituted acetylenes :



Very valuable contributions have also been made by (Sir) I. M. Heilbron, E. R. H. Jones, and their colleagues. Of particular interest is the reaction between sodium acetylide and *epichlorohydrin* in liquid ammonia.⁷⁴ The product is rather unexpectedly the acetylenic-ethylenic primary alcohol, pentenynol (XIX), formed probably by the rearrangement of (XVIII). (XIX) undergoes a large number of reactions of synthetic value; e.g., by hydration with sulphuric acid and mercuric sulphate it readily gives 2-methylfuran (XX).



Benzopyrylium salts including flavylium salts and some pyrylium salts have been synthesised by A. W. Johnson and R. R. Melliush ⁷⁵ by a new

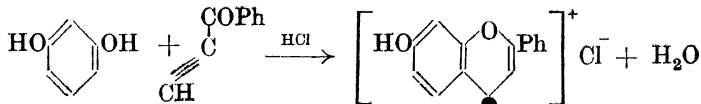
⁷⁴ L. J. Haynes, (Sir) I. M. Heilbron, E. R. H. Jones, and F. Sondheimer, *J.*, 1947, 1583, 1586.

⁷⁵ *J.*, 1947, 346.

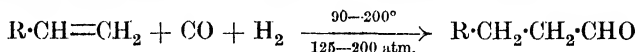
* The precise formulation of a possible intermediate presents difficulties. An addition compound of $\text{CH}\equiv\text{CH}$ and CO may perhaps be represented in one of its canonical forms as $\text{CH}=\text{CH}^-$.



method which consists of interaction of phenols with ethynyl ketones ⁷⁶ in the presence of acids :



Use of Carbon Monoxide in Organic Synthesis.—A review of numerous applications of carbon monoxide is given by A. Willemart.⁷⁷ Reference is made to the preparation of acetic acid by the catalysed addition of carbon monoxide to methyl alcohol. In this review and elsewhere (Otto Roelen ⁷⁸) an account is given of the catalysed addition of carbon monoxide and hydrogen to olefins. Roelen recommended catalysts containing cobalt, thorium oxide, kieselguhr, and copper, the reaction being :



Apart from commercial utilisation, the process (the "oxo" reaction) is of considerable potential value in organic syntheses, for it is a means of converting an olefin into a primary alcohol. Further details of the process have been recently worked out by H. Adkins and G. Krsek ⁷⁹ who show that an excellent catalyst is an ethereal solution of dicobalt octacarbonyl $[\text{Co}(\text{CO})_4]_2$, the preparation of which they describe. Some of their results of this reaction (which is virtually the addition of H and CHO across the double bond) are as follows, yields being from 50% upwards :

| Olefin. | Product. |
|------------------|-----------------------------------|
| Styrene | Hydrotropaldehyde |
| Ethyl crotonate | Ethyl β -formylbutyrate |
| Diethyl fumarate | Diethyl α -formylsuccinate |
| Allyl alcohol | γ -Hydroxybutaldehyde |
| Allyl acetate | γ -Acetoxybutaldehyde |
| Ethyl acrylate | β -Carbethoxypropaldehyde |
| Pent-2-ene | Hexaldehydes (mixed) |

This formylation process has also been carefully investigated by Dutch workers ⁸⁰ who carried out the reaction in a rotating autoclave in the presence of a cobalt catalyst. The aldehydes thus obtained, when hydrogenated in the same autoclave with the same catalyst with pure hydrogen instead of water gas, gave primary alcohols. These authors have deduced a number of rules which appear to make it possible to predict the structure of the alcohols which can be obtained from a given olefin.

What promises to be an important reaction is the ready synthesis of carboxylic acids (and their derivatives) from an olefin and carbon monoxide, with nickel carbonyl as catalyst at 200—300°/150—300 atm.⁸¹ This process

⁷⁶ K. Bowden, (Sir) I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J.*, 1946, 39.

⁷⁷ *Bull. Soc. chim.*, 1947, 14, 152.

⁷⁸ U.S.P. 2,327,066.

⁷⁹ *J. Amer. Chem. Soc.*, 1948, 70, 383.

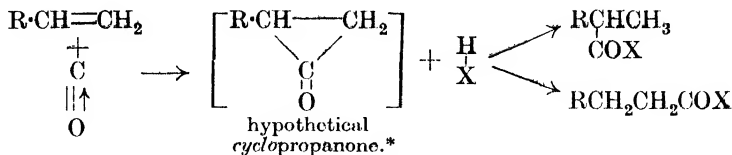
⁸⁰ A. I. M. Keuhemans, A. Kwantes, and T. van Bavel, *Rec. Trav. chim.*, 1948, 67, 298.

⁸¹ BIOS, Item 22.

is, of course, an extension of the corresponding reaction with acetylene cited above :

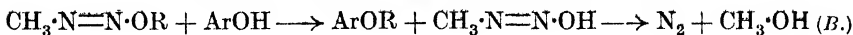
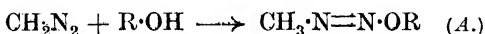


General reactions of this type may be summarised as follows ($\text{X} = \text{H}, \text{OH}, \text{OR}, \text{NH}_2, \text{O}\cdot\text{COR}_1$).



Hydroxylation.—Many unsaturated compounds are hydroxylated effectively and rapidly by performic acid. Thus oleic acid is converted at room temperature into 9 : 10-dihydroxystearic acid.⁸² No epoxy-compound is obtained, although it is likely that this is the initial product of the reaction. Recently the best methods for preparing the reagent have been examined, and J. English and J. D. Gregory⁸³ recommend for most hydroxylations a performic acid solution made from 98 to 100% formic acid, 90% hydrogen peroxide, and a trace of sulphuric acid.

Alkylation.—It is often observed that certain hydroxylic compounds resist methylation by an ethereal solution of diazomethane. A. Schönberg and A. Mustafa⁸⁴ have made the very useful observation that many such compounds (*e.g.*, methyl salicylate and *o*-hydroxyacetophenone) are readily methylated if methyl alcohol is added to the ethereal solution of diazomethane. It is possible that, in methyl-alcoholic solution, diazomethane coexists with a compound formed as in *A* ($\text{R} = \text{Me}$), which then acts as a very powerful methylating agent according to scheme *B* :



Confirmation of this view seems to be afforded by the fact that other alcohols can be used instead of methyl alcohol. Thus these authors treated stilboestrol with ethereal diazomethane containing *n*-propyl alcohol and obtained the pure di-*n*-propyl ether.

P. H. Given and D. Ll. Hammick have studied some catalysed gas-phase reactions of aromatic hydrocarbons. They have shown⁸⁵ that methyl ether reacts with benzene at 400–500° in the presence of metal oxide catalysts to give toluene and polymethylenes in about 70% yield. Methanol can also be used, but less effectively, as a methylating agent in

⁸² D. Swern, G. N. Billen, and T. W. Frudley, *J. Amer. Chem. Soc.*, 1945, **67**, 1786.

⁸³ *Ibid.*, 1947, **69**, 2120.

⁸⁴ *J.*, 1946, 746.

⁸⁵ *J.*, 1947, 928.

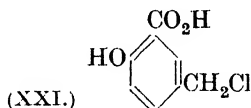
* Perhaps as $\text{R}\cdot\text{CH}-\text{CH}_2$ and $\text{R}\cdot\text{CH}-\text{CH}_2$. See footnote, p. 133. A different

mechanism is suggested by A. du Pont *et al.* (*Bull. Soc. chim.*, 1948, **15**, 529).

gas-phase reactions,⁸⁶ and in addition it is known that methanol is rapidly converted into methyl ether and water in the presence of certain metal-oxide catalysts.⁸⁷ It does not, however, seem possible to deduce with certainty whether methyl ether or methanol is the actual methylating agent. It should, however, be noted that N. M. Cullinane and S. J. Chard have successfully converted naphthalene into 2-methylnaphthalene⁸⁸ by causing naphthalene and methanol to react in contact with aluminosilicate catalysts in the vapour phase. The methylation of naphthalene by methyl ether in the presence of bauxite gives a mixture of 1- and 2-methylnaphthalenes in low yield.⁸⁹

Many aromatic compounds have been alkylated by alcohols in the presence of phosphoric acid⁹⁰ and perchloric acid.⁹¹ Benzene is isopropylated at its boiling point in the presence of phosphoric oxide and boron trifluoride.⁹²

Chloromethylation. Work continues on this valuable process. Benzyl chloride⁹³ is obtained in 70—78% yield from benzene, paraformaldehyde, and hydrogen chloride at 50° (1 atm., 75 minutes) in the presence of zinc chloride as catalyst. Several useful variations of this process are recorded.⁹⁴ Phenol dissolved in concentrated hydrochloric acid and treated with 40% formalin in the presence of sulphuric acid, zinc chloride, etc., is chloromethylated. Salicylic acid⁹⁵ gives a good yield of (XXI). The chloromethylation of naphthalene and tetralin⁹⁶ and of chloronaphthalene⁹⁷



has been described. Glycols have been chloromethylated by passing hydrogen chloride into a mixture of the glycol and trioxymethylene.⁹⁸

*Aminomethylation*⁹⁹ (introduction of the $\text{CH}_2\cdot\text{NH}_2$ group) of thiophen is brought about by the action of formaldehyde and ammonium chloride.

⁸⁶ Jenkins, B.Sc. Thesis, Oxford, 1940.

⁸⁷ H. Adkins and P. D. Perkins, *J. Physiol. Chem.*, 1928, **32**, 221.

⁸⁸ *J.*, 1948, 804.

⁸⁹ (Miss) G. P. Armstrong, D. H. Grove, D. Ll. Hammick, and H. W. Thompson, *ibid.*, p. 1700.

⁹⁰ I. P. Tzukurvanik, *J. Gen. Chem. Russia*, 1945, **15**, 699.

⁹¹ C. A. Sears, *J. Org. Chem.*, 1948, **13**, 120.

⁹² G. Vermillion and M. A. Hill, *J. Amer. Chem. Soc.*, 1945, **67**, 2209.

⁹³ A. Ginsberg *et al.*, *Ind. Eng. Chem.*, 1946, **38**, 478.

⁹⁴ G. Lock, *Ber.*, 1941, **74**, 1568; T. Maki *et al.*, *J. Soc. Chem. Ind. Japan*, 1947, **47**, 452.

⁹⁵ C. A. Bushler, *J. Tennessee Acad. Sci.*, 1947, **22**, 303.

⁹⁶ G. M. Badger, J. W. Cook, and A. W. Crosbie, *J.*, 1947, 1432.

⁹⁷ D. H. S. Horn and F. L. Warren, *J.*, 1946, 144.

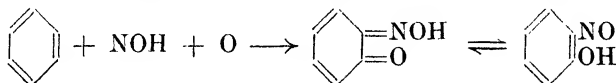
⁹⁸ J. Lichtenberger and L. Martin, *Bull. Soc. chim.*, 1945, **12**, 114.

⁹⁹ H. D. Hartough, S. J. Linkasiewicz, and E. H. Murray, *J. Amer. Chem. Soc.*, 1946, **68**, 1389.

This reaction, which appears to be general for thiophen derivatives, is superficially similar to the Mannich reaction.

Sulphomethylation ¹⁰⁰ (replacement of H by $\text{CH}_2\cdot\text{SO}_3\text{Na}$), which seems to be of rather limited application, is effected by aqueous formaldehyde and excess of sodium sulphite. Thus β -naphthol gives $2 : 1\text{-OH}\cdot\text{C}_{10}\text{H}_6\cdot\text{CH}_2\cdot\text{SO}_3\text{Na}$.

Nitrosation and Nitration.—*Nitrosation.* The usual nitrosation of phenols leads to the formation of *p*-nitrosophenols. Therefore the publications of O. Baudisch ¹⁰¹ are of particular interest. The Baudisch reaction consists in the utilisation of the "nitrosyl" radical, NOH, and an oxidising agent, whereby it is possible to introduce in one reaction both the nitroso- and the hydroxyl group, in the ortho-position, into the benzene ring :



The presence of a copper salt is essential for the reaction, both to stabilise the NOH radical and to ensure the formation of an *o*-compound to the exclusion of the *p*-compound. The NOH is formed either by the reduction of nitrous acid or by the oxidation of hydroxylamine. Recently G. Cronheim ¹⁰² has successfully exploited the Baudisch reaction and has prepared numerous *o*-nitrophenols and described their properties, in particular the formation of complex metallic salts.

A superficially analogous process is the combined oxidation and nitration of benzene in one operation, with production of $2 : 4$ -dinitrophenol and picric acid. The reagent is a solution of mercuric nitrate in nitric acid, and the process is known as "oxynitration." The idea, ¹⁰³ an old one, has been extensively developed ¹⁰⁴ during the Second World War, and various mechanisms have been suggested for the reaction. Nothing very definite has emerged, but the suggestion of E. E. Aristoff *et al.* ¹⁰⁵ that nitrosobenzene is an intermediate is attractive. In view of the evolution of oxides of nitrogen during the reaction, the Reporter feels that a mechanism similar to that of the Baudisch reaction may be worthy of consideration.

Nitration can be accomplished without using sulphuric acid if a suitable diluent is added to remove water by the customary azeotropic distillation technique. ¹⁰⁶ In nitrating benzene, excess of benzene is used to remove the water formed in the course of the reaction. Naphthalene is converted into 1-nitronaphthalene by using 50% nitric acid and light petroleum (b. p. $30\text{--}60^\circ$). These reactions are of interest in view of the extensive work being carried out with nitric acid-sulphuric acid mixtures.

¹⁰⁰ C. M. Suter, R. K. Bair, and F. G. Bordwell, *J. Org. Chem.*, 1945, **10**, 470.

¹⁰¹ *Naturwiss.*, 1939, **27**, 768, 769; *Science*, 1940, **92**, 336; *J. Amer. Chem. Soc.*, 1941, **63**, 672.

¹⁰² *J. Org. Chem.*, 1947, **12**, 1, 7, 20.

¹⁰³ R. Wolfenstein and O. Boeters, D.R.-P. 194,883 (August 1906).

¹⁰⁴ F. H. Westheimer, E. Segel, and R. Schramm, *J. Amer. Chem. Soc.*, 1947, **69**, 773; W. E. Backmann, J. M. Chenerda, N. E. Reno, and E. C. Horning, *J. Org. Chem.*, 1948, **13**, 390.

¹⁰⁵ *Ind. Eng. Chem.*, 1948, **40**, 1281.

¹⁰⁶ U.S.P. 2,435,314, 2,435,544.

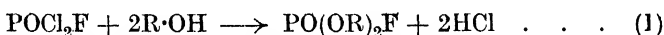
General Reactions of Phosphorus Compounds.—Since the last report on this subject,¹⁰⁷ several important general methods have been described. Acetyl peroxide or benzoyl peroxide permits the ready addition of phosphorus trichloride to $\text{CHR}:\text{CH}_2$ at 85° (in nitrogen) to give $\text{CHRCI}\cdot\text{CH}_2\cdot\text{PCl}_2$.¹⁰⁸ Addition of phosphorus pentachloride to a styrene, and subsequent hydrolysis, yields an unsaturated phosphonic acid, $\text{R}\cdot\text{CH}=\text{CH}\cdot\text{PO}_3\text{H}_2$.¹⁰⁹

Ethylene oxide reacts with phosphorus trichloride¹¹⁰ and phosphorus tribromide. The former gives all three possible derivatives, $\text{R}\cdot\text{O}\cdot\text{PCl}_2$, $(\text{R}\cdot\text{O})_2\text{PCl}$, and $(\text{R}\cdot\text{O})_3\text{P}$ ($\text{R} = \text{CH}_2\text{Cl}\cdot\text{CH}_2$).

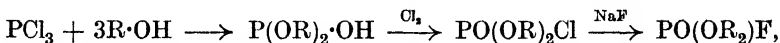
A. R. Todd and his colleagues have continued work on phosphorylation. They now find that a dialkyl hydrogen phosphite in the presence of trichlorobromomethane will phosphorylate even aromatic amines directly, and in the presence of a suitable tertiary base will phosphorylate ethyl alcohol. A mechanism is suggested involving the intermediate formation of a halogenophosphonate.¹¹¹ The use of dibenzyl chlorophosphonate and subsequent hydrogenolysis to remove the benzyl groups¹¹² has enabled J. Baddiley and A. R. Todd to synthesise muscle adenylic acid, adenosine diphosphate,¹¹³ and adenosine triphosphate.¹¹⁴

Triarylphosphines are readily converted by aryl bromides and aluminium chloride into tetra-arylphosphonium salts. Similar reactions lead also to synthesis of arsonium and stibonium salts.¹¹⁵

A method of very wide application for the preparation of a variety of derivatives of fluorophosphonic acid has been devised by B. C. Saunders¹¹⁶ and his co-workers. They find that phosphorus oxydichlorofluoride will react smoothly with alcohols, phenols, thiols, and primary and secondary amines :



Reaction (1) provides an alternative to :



another general method from phosphorus trichloride *via* the hydrogen phosphite.¹¹⁷ Many of the alkyl fluorophosphonates are powerful inhibitors of

¹⁰⁷ *Ann. Reports*, 1945, **42**, 103.

¹⁰⁸ M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Amer. Chem. Soc.*, 1945, **67**, 1864.

¹⁰⁹ G. M. Kosolapoff and W. F. Huber, *ibid.*, 1946, **68**, 2540; see also E. Bergmann and A. Bondi, *Ber.*, 1930, **63**, 1158.

¹¹⁰ M. I. Kabachnik and P. A. Rossiiskaya, *Otdel. Khim. Nauk*, 1946, 295; *Bull. Acad. Sci. U.R.S.S., Classe Sci. Chim.*, 1947, 389.

¹¹¹ F. R. Atherton and A. R. Todd, *J.*, 1947, 674.

¹¹² F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J.*, 1945, 382.

¹¹³ J. Baddiley and A. R. Todd, *J.*, 1947, 648.

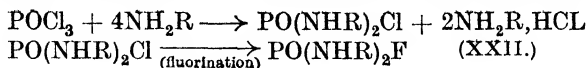
¹¹⁴ J. Baddiley, A. M. Michelson, and A. R. Todd, *Nature*, 1948, **161**, 761.

¹¹⁵ F. G. Mann *et al.*, *J.*, 1940, 1192; 1942, 666; 1947, 505.

¹¹⁶ N. B. Chapman and B. C. Saunders, *J.*, 1948, 1010; R. Heap and B. C. Saunders, *ibid.*, p. 1313; B. C. Saunders *et al.*, B.P. 602,446.

¹¹⁷ B. C. Saunders and G. J. Stacey, *J.*, 1948, 695; B.P. 601,210; H. McCombie and B. C. Saunders, *Nature*, 1946, **157**, 287, 776.

cholinesterase, and some (e.g., diisopropyl fluorophosphonate or D.F.P.) are finding clinical application.¹¹⁸ Fluoroaminophosphine oxides (XXII) are also readily prepared from primary and secondary amines as follows:¹¹⁹



Some of these products show promise as insecticides.

B. C. S.

3. HOMOLYTIC REACTIONS.

In the four years which have elapsed since the last report on this subject,¹ many further examples have been recorded of reactions involving free radicals and atoms which result from the symmetrical fission of a covalent bond, and reactions of this type now occupy a much larger place within any comprehensive theory of organic reactions than seemed probable ten years ago. In the period under review two important books on free-radical chemistry have been published^{2,3} which cover different aspects of the subject, and in 1947 a Discussion on "The Labile Molecule" was held by the Faraday Society,⁴ which dealt with fundamental theory, reactions in both the gas and the liquid phase, and polymerisation. It is probably in polymerisation chemistry that the greatest advances in this subject have been made. Developments in this technically important field have in fact been so rapid and far-reaching that no attempt can be made to include them in the present report, although it is pertinent to recall that much of our present-day knowledge of polymerisation, particularly with reference to the phenomena of activation, inhibition, retardation, and chain transfer, can be traced back to exploratory chemical investigations on the occurrence of free radicals as transient intermediates in many organic reactions in solution carried out more than ten years ago.^{5,6} It is now well established that addition polymerisation can take place by two different mechanisms. Catalysts such as benzoyl peroxide initiate the free-radical or homolytic mechanism, whereas with catalysts such as stannic chloride or boron trifluoride an ionic or heterolytic mechanism is called into play. One of the most interesting features of recent developments is the unmistakable evidence of a similar duality of function in many compounds which, under appropriate conditions, can take part in either a homolytic or a heterolytic process.

¹¹⁸ (Sir) L. Whitby, *Fractioner*, 1947, **159**, 243; J. P. Quilliam and T. A. Quilliam, *Medical Press*, 1947, October 22nd.

¹¹⁹ H. McCombie and B. C. Saunders, Report No. 16 to Min. Supply, 1943; *Nature*, 1946, **157**, 776.

¹ D. H. Hey, *Ann. Reports*, 1944, **41**, 181.

² W. A. Waters, "The Chemistry of Free Radicals," Clarendon Press, Oxford, 1946.

³ E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publishing Corporation, New York, 1946.

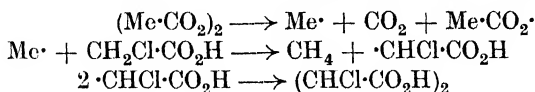
⁴ Faraday Society Discussion, 1947, **2**.

⁵ D. H. Hey and W. A. Waters, *Chem. Reviews*, 1937 **21**, 169.

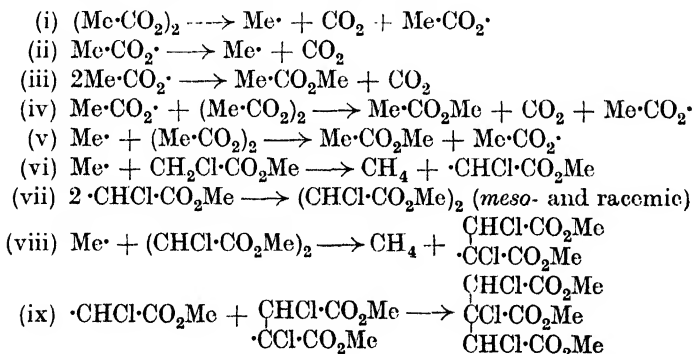
⁶ C. C. Price, *Ann. New York Acad. Sci.*, 1943, **44**, 351.

Such compounds are the halogens, hydrogen halides, thiols, *N*-bromo-succinimide, hydrogen peroxide, Grignard reagents, and certain diazo-compounds in which the alternative processes are facilitated by the existence of tautomeric forms. The two mechanisms usually but not always lead to different products.

Reactions of Peroxides.—It was reported by M. S. Kharasch and M. T. Gladstone ⁷ that, when acetyl peroxide decomposes in glacial acetic acid at 95–100°, methane, carbon dioxide, and succinic acid are formed, and that, in a similar manner, *isobutyric* acid and chloroacetic acid give tetramethylsuccinic acid and *mesodichlorosuccinic* acid respectively. The series of reactions with chloroacetic acid may be represented as follows :



Since exclusive formation of the *meso*-form by dimerisation of the free radical $\cdot\text{CHCl}\cdot\text{CO}_2\text{H}$ is not to be expected, the reaction was further investigated by M. S. Kharasch, E. V. Jensen, and W. H. Urry, ⁸ with the result that both *meso*- and racemic dichlorosuccinic acid were found to be present in approximately equal amounts. Reactions were also carried out between acetyl peroxide and (*a*) methyl chloroacetate and (*b*) *isobutyryl* chloride. In (*a*) the products included methane, carbon dioxide, methyl acetate, chloroacetic acid, methyl dichlorosuccinate, and trimethyl $\alpha\alpha'\beta$ -trichlorotricarballylate, which are formed as follows :

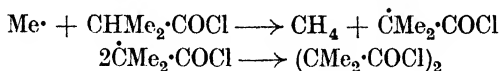


The formation of more than one molecular proportion of both carbon dioxide and methane for each molecule of peroxide is explained by reactions (i) and (ii), and the production of more carbon dioxide than methane by reactions (iii) and (iv). Since the amount of the tribasic ester formed is greater than would be expected on a statistical basis, the free methyl radical is regarded as being selective in its action and is sufficiently stable not to react with the first molecule encountered. Many other examples are known in which a free radical reacts preferentially with a tertiary hydrogen atom.

⁷ *J. Amer. Chem. Soc.*, 1943, **65**, 15.

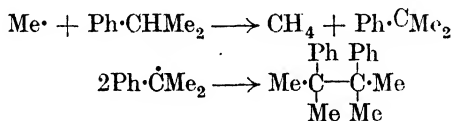
⁸ *J. Org. Chem.*, 1945, **10**, 386.

In the reaction between acetyl peroxide and *isobutyryl* chloride the products include methane, carbon dioxide, methyl acetate, acetyl chloride, and tetramethylsuccinic anhydride, which again demonstrates the selective action of the methyl radical on the tertiary hydrogen atom, thus :



Side reactions during the isolation of the products account for the formation of acetyl chloride and the conversion of the tetramethylsuccinyl chloride into the anhydride. These results show the usefulness of acetyl peroxide as a reagent for bringing about the linking of α - to α - and β - to β -carbon atoms in aliphatic acids and their derivatives. The peroxides of longer-chain acids and of aromatic acids are more stable and are not suitable for these reactions.

Further examples of the selective action of the methyl radical were provided by M. S. Kharasch, H. C. McBay, and W. H. Urry,⁹ who in similar manner from the methyl esters of dichloroacetic acid, acetoacetic acid, succinic acid, and phenylacetic acid obtained the methyl esters of tetrachlorosuccinic acid, diacetylsuccinic acid, 1 : 2 : 3 : 4-butanetetracarboxylic acid (*meso*- and racemic) and diphenylsuccinic acid (*meso*- and racemic). They also showed¹⁰ that the methyl radical, generated from acetyl peroxide, has a selective action on the hydrogen atoms attached to the side chain in alkylbenzenes, giving rise to free radicals which readily dimerise. Thus, *isopropylbenzene* gives 2 : 3-diphenyl-2 : 3-dimethylbutane in almost quantitative yield :



In similar manner ethylbenzene gives 2 : 3-diphenylbutane (*meso*- and racemic), and *p*-methoxy-*n*-propylbenzene gives a mixture of the *meso*- and racemic forms of hexoestrol methyl ether, but, since the methyl radical seeks preferentially a hydrogen atom attached to the α -carbon atom, further reactions occur which lead to the formation of polymers.

A study has been made¹¹ of the action of α - and β -naphthoyl peroxide on carbon tetrachloride. These reactions follow closely the corresponding reaction of benzoyl peroxide on carbon tetrachloride.¹² In a study of the action of acetyl peroxide on a series of aliphatic ketones, M. S. Kharasch, H. C. McBay, and W. H. Urry¹³ have developed a new method for the synthesis of symmetrical 1 : 4-diketones which is a logical extension of their earlier work on acids and esters and further illustrates the selective

⁹ *J. Org. Chem.*, 1945, **10**, 394.

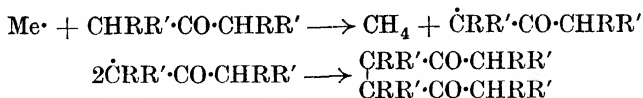
¹⁰ *Ibid.*, p. 401.

¹¹ M. S. Kharasch and R. L. Dannley, *ibid.*, p. 406.

¹² J. Boeseken and H. Gelissen, *Rec. Trav. chim.*, 1924, **43**, 869.

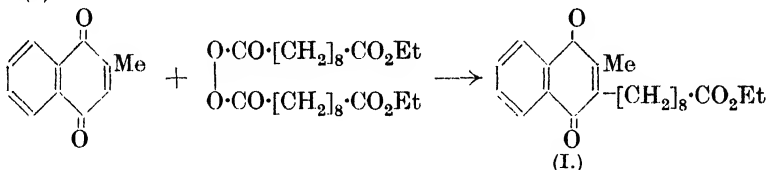
¹³ *J. Amer. Chem. Soc.*, 1948, **70**, 1269.

action of the methyl radical, which reacts with hydrogen atoms in the order tertiary > secondary > primary. This method may be represented as follows :



Since, however, the final 1:4-diketone also contains tertiary hydrogen atoms at α -positions, further reactions with methyl radicals can ensue with the formation of tri- and tetra-ketones. The relative yields of the various ketones depend primarily on the ratio of ketone to peroxide used, and when a large excess of the ketone is used the formation of the 1:4-diketone predominates.

The use of acyl peroxides for the alkylation of quinones, introduced by L. F. Fieser and A. E. Oxford, has already been reported.¹⁴ Many further examples of this useful reaction have now been recorded. L. F. Fieser and R. B. Turner¹⁵ have shown that, when 2-methylnaphthaquinone is heated with succinyl peroxide in acetic acid solution, β -(2-methylnaphtha-3-quinonyl) propionic acid is obtained. In similar manner treatment with glutaryl peroxide gives γ -(2-methylnaphtha-3-quinonyl)butyric acid, while the peroxide derived from the half-ester of sebacic acid gives the pelargonic ester (I) :



Similar reactions were carried out by L. F. Fieser and E. M. Chamberlin¹⁶ with 2:5-dihydroxybenzoquinone and lauryl peroxide, tridecyl peroxide, myristyl peroxide and erucyl peroxide by means of which fatty side-chains were introduced into the 3-position. The product derived from the reaction with lauryl peroxide was identified as embelin, and that from myristyl peroxide as rapanone. Many further examples of the use of this reaction for the preparation of 2-hydroxy-3-alkylnaphthaquinones have been reported by Fieser and his co-workers¹⁷ in their search for naphthaquinone antimalarials. The reaction between the peroxide derived from *cis*- γ -(4-acetoxycyclohexyl)butyric acid and 2-hydroxy-1:4-naphthaquinone, which introduces the *cis*- γ -(4-acetoxycyclohexyl)propyl group into the 3-position, has also been reported.¹⁸

The properties of the phenylvinylmethyl radical, which results from the action of acetyl peroxide on allylbenzene, have been studied by H. P. Koch,¹⁹ who has shown that on dimerisation it gives rise to both dicinnamyl (1:6-

¹⁴ Ref. 1, p. 191.

¹⁵ *J. Amer. Chem. Soc.*, 1947, **69**, 2338.

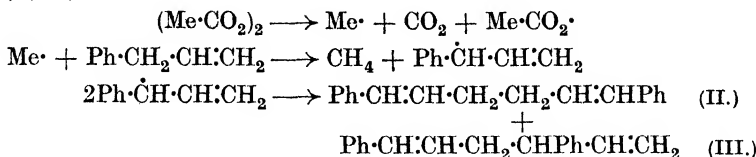
¹⁶ *Ibid.*, 1948, **70**, 71.

¹⁷ *Ibid.*, pp. 3174 *et seq.*

¹⁸ W. G. Dauben and R. E. Adams, *ibid.*, p. 1761.

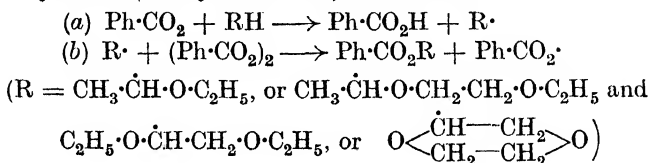
¹⁹ *J.*, 1948, 1111.

diphenylhexa-1:5-diene) (II) and isodicinnamyl (1:4-diphenylhexa-1:5-diene) (III), thus :

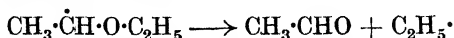


No 3:4-diphenylhexa-1:5-diene is formed, the *meso*-form of which gives a similar mixture of dicinnamyl and isodicinnamyl on thermal rearrangement at temperatures above 100°.

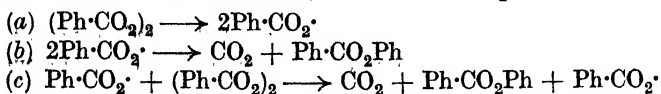
The reactions of benzoyl peroxide with certain ethers have been investigated by W. E. Cass,²⁰ who postulates the chain mechanism represented by (a) and (b) to account for the rapid decomposition in diethyl ether, ethylene glycol diethyl ether (diethyl cellosolve), and dioxan :



With diethyl ether at 37° the main products are carbon dioxide, benzoic acid, and 1-ethoxyethyl benzoate, and, with ethylene glycol diethyl ether at 40°, carbon dioxide, benzoic acid, and a mixture of 1-(2-ethoxyethoxy)-ethyl benzoate and 1:2-diethoxyethyl benzoate, which are the products to be expected from reactions (a) and (b). With dioxan at 40° the results are less clear, but carbon dioxide and benzoic acid are formed together with dioxanyl benzoate. The formation of 1-ethoxyethyl benzoate from diethyl ether, in almost quantitative yield, shows that hydrogen is taken preferentially from a methylenic carbon atom, and that there must have been very little decomposition of type :



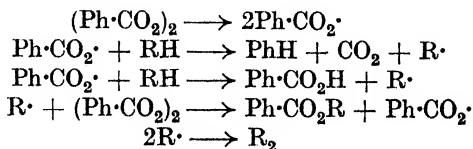
In a study of the kinetics of the decomposition of benzoyl peroxide in a wide range of solvents, K. Nozaki and P. D. Bartlett²¹ have pointed out that, although the decomposition is so nearly unimolecular that it is usually treated as such, nevertheless the rate definitely varies with concentration. They observed that the decomposition could be induced by free radicals, and suggested that the reaction is induced in part by the radicals which are normally present in a solution of decomposing benzoyl peroxide. This means that a reaction of higher order accompanies the unimolecular decomposition, and all the observed products of the decomposition can be accommodated within such a scheme, which can be represented as follows :



²⁰ *J. Amer. Chem. Soc.*, 1947, **69**, 500.

²¹ *Ibid.*, 1946, **68**, 1686.

In general, the benzoyloxy-radicals will attack the solvent, and, if such attack results in new free radicals which are more stable and less reactive than benzoyloxy-radicals (*i.e.*, chain transfer), the effect of the solvent would be to suppress the chain decomposition (*c*). If, however, new radicals of comparable activity are formed the process will affect only the products formed and not the overall kinetics. The fact that part of the decomposition of benzoyl peroxide in a solvent is of chain character is shown by the facts that it responds to inhibitors and can be induced with known free radicals. It was found that the rate of decomposition could be represented by the equation $-\frac{dC}{dt} = k_1C + k_iC^{3/2}$, in which C is the peroxide concentration, k_1C is the component of the rate due to the primary step, and $k_iC^{3/2}$ is the component representing the part induced by free radicals, and the results showed that the induced decomposition is the main factor responsible for the variation in rate from one solvent to another. The same authors²² have investigated further the decomposition of benzoyl peroxide in ethers, as well as in other solvents such as alcohols, phenols, and amines. In the ether series at 79.8° a considerable variation in the rate of decomposition was observed, and whereas in diethyl ether the reaction is more than 60% complete within five minutes, in anisole and diphenyl ether, which behave as normal aromatic solvents, the reaction is less than 15% complete in one hour. The rates of decomposition are also rapid in alcohols and in phenols, but are of the same order of magnitude as in the ethers. Variations are observed within each series. Amines induce a very rapid reaction which may become explosive. These authors conclude that chain reactions are involved, as shown by oxygen inhibition and retardation by reaction products, and that the intermediate radicals formed are more reactive to benzoyl peroxide than are benzoyloxy-radicals. The latter assumption is rendered necessary to explain the accelerated rates of decomposition in certain solvents, if it be assumed that the rate of the spontaneous truly unimolecular decomposition is about the same in all solvents. The reactions are very close to first order with respect to peroxide. The effect of temperature and solvent upon the decomposition of benzoyl peroxide has also been investigated by P. F. Hartman, H. G. Sellers, and D. Turnbull,²³ who gave the following scheme which, however, is considered by them to be an over simplification for most solvents :

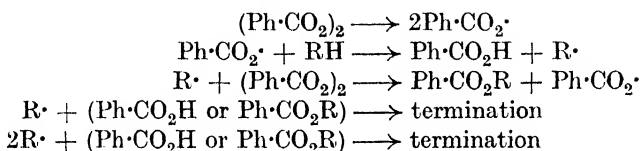


The solvents used by these workers were benzene, *tert.*-butylbenzene, *cyclo*-hexane, methyl*cyclo*hexane, and *n*-octane. The kinetics of the decompos-

²² *J. Amer. Chem. Soc.*, 1947, **69**, 2299.

²³ *Ibid.*, p. 2416.

ition of benzoyl peroxide in solvents have also been investigated by W. E. Cass,²⁴ who directed attention to the fact that the first-order constants were found to increase with higher initial peroxide concentrations, a characteristic which was especially noticeable in mixed solvents such as vinyl acetate-benzene and styrene-toluene. By measuring the rates of decomposition in various solvents at 30° in absence of air it was shown that the reaction was not a simple unimolecular process. With aromatic solvents, chloroform, and carbon tetrachloride no acceleration of the process was observed, which is taken to mean that any free radicals derived from these solvents do not react appreciably with unchanged peroxide, but with dioxan and ethylene glycol diethyl ether an acceleration was noted, which was susceptible to inhibition and suggested the occurrence of the following reaction chains :



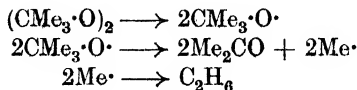
This treatment differs from that of Nozaki and Bartlett,²¹ who include that portion of the peroxide which undergoes the spontaneous unimolecular decomposition as well as the chain reaction, but the general conclusions in both papers concerning the existence of the chain reaction are similar. A study of the effects of temperature, solvent, and halogen-substitution in the benzene nucleus on the rate of decomposition of benzoyl peroxide has been made by D. J. Brown,²⁵ who concluded that, after a preliminary period, there followed two parallel reactions of first and second order. This suggested an initial dissociation of the peroxide followed by a further dissociation of the hemimer and a parallel reaction of the hemimer as an oxidising agent. The almost constant order of reaction with change in environment and with halogen substitution in the benzene nucleus indicated a uniform mechanism. Convincing evidence for a free-radical dissociation is provided by the comparatively large variation in rate constant with temperature and the marked insensitivity to changes in the dielectric constant of the solvent. Further, the rates of decomposition of substituted benzoyl peroxides are not directly related to the ionisation constants of the corresponding carboxylic acids.

Considerable attention has been devoted to the reactions of *tert.*-butyl peroxide, which is one of the most stable of the known alkyl peroxides. It can be readily prepared from *tert.*-butyl alcohol or *isobutylene* and sulphuric acid (*i.e.*, from *tert.*-butyl hydrogen sulphate) in the presence of 30% hydrogen peroxide, and can be distilled at atmospheric pressure without decomposition. It does not respond to the usual tests for peroxides, and is even resistant to hydrogenation, but at high temperatures it is a very active polymerisation catalyst. At temperatures between 200° and

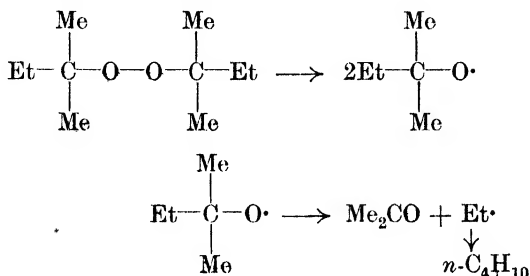
²⁴ *J. Amer. Chem. Soc.*, 1946, **68**, 1976.

²⁵ *Ibid.*, 1948, **70**, 1208.

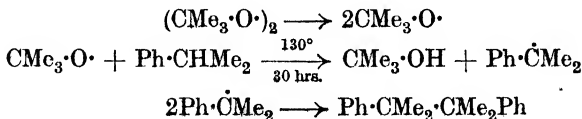
300° it gives acetone and ethane, which are considered to be formed as follows : ²⁶



tert.-Butyl hydroperoxide is also one of the most stable hydroperoxides, but it loses oxygen at 95—100°, and decomposes explosively at 250°. With acid chlorides it gives rise to stable per-esters which have unusual properties as polymerisation catalysts.²⁷ *tert.*-Amyl peroxide, which has been prepared from *tert.*-amyl hydrogen sulphate and hydrogen peroxide, shows properties similar to those of *tert.*-butyl peroxide, and at 250° it gives mainly acetone and *n*-butane with small amounts of methyl ethyl ketone and a mixture of ethane and propane, which shows the preferential elimination of the heavier alkyl group, thus : ²⁸



The kinetics of the pyrolysis of *tert.*-butyl and *tert.*-amyl peroxides have been investigated by J. H. Raley, F. F. Rust, and W. E. Vaughan.²⁹ In the vapour phase the decomposition of *tert.*-butyl peroxide is correctly represented as given above, the stable products being acetone and ethane, but in solution in *isopropylbenzene* at 130° some 2 : 3-diphenyl-2 : 3-dimethylbutane is formed as follows :



The formation of 2 : 3-diphenyl-2 : 3-dimethylbutane recalls the reaction which takes place between methyl radicals, generated from acetyl peroxide, and *isopropylbenzene* previously reported by M. S. Kharasch, H. C. McBay, and W. H. Urry.¹⁰ Pyrolysis of *tert.*-butyl peroxide at 140—160° is a homogeneous first-order non-chain reaction, and all the products can be accounted for by the intermediate formation of *tert.*-butoxy- and methyl radicals, and, in the case of *tert.*-amyl peroxide, of *tert.*-amyloxy-, methyl, and ethyl radicals. The usefulness of *tert.*-alkyl peroxides in the study of

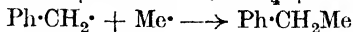
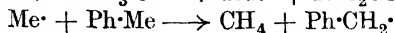
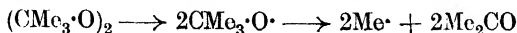
²⁶ N. A. Milas and D. M. Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205.

²⁷ *Idem*, *ibid.*, p. 642.

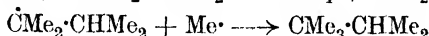
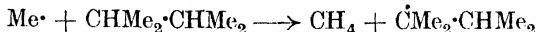
²⁸ *Idem*, *ibid.*, p. 643.

²⁹ *Idem*, 1948, **70**, 88.

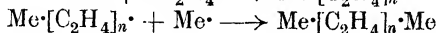
free-radical phenomena has been further demonstrated by F. F. Rust, F. H. Seubold, and W. E. Vaughan,³⁰ who showed that in reactions with toluene and 2 : 3-dimethylbutane in the gas phase at 200—235° the products are ethylbenzene and 2 : 2 : 3-trimethylbutane (triptane) respectively :



and

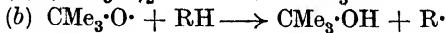


With unsaturated compounds the reactions are more complex. Addition of methyl to ethylene gives propyl, which may add to another ethylene molecule, and the reaction can proceed with yet further molecules of ethylene (unless or until the chain is terminated by collision with a second alkyl radical) thus :



This mechanism is strikingly confirmed by the isolation of hydrocarbons with only an even number of carbon atoms from the reaction between methyl and ethylene. Addition of methyl to propylene can give two new radicals, each of which can either (a) combine with a methyl radical, (b) abstract hydrogen from propylene, (c) combine with radicals other than methyl, or (d) add to propylene.

With regard to the kinetics of the decomposition of *tert.*-butyl peroxide in the liquid phase it has been shown³¹ that, in contrast to the behaviour of benzoyl peroxide, *tert.*-butyl peroxide shows the same rate of decomposition at 135° in cumene, *tert.*-butylbenzene and tri-*n*-butylamine, which is similar to that found in the vapour phase. This implies a common simple rate-determining dissociation process, and although the rates in different solvents are similar the ratio of *tert.*-butyl alcohol to acetone formed varies. These reactions can be represented as follows, from which it will be evident that (b) and (c) are competitive :

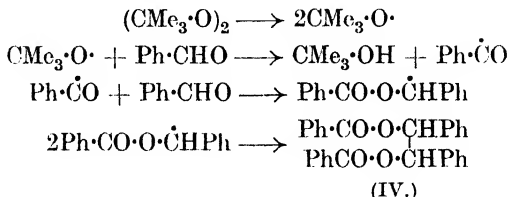


The common rate-determining unimolecular reaction is the scission of the oxygen-oxygen bond, as represented in (a). With increase in temperature reaction (c) is preferred to reaction (b). The normal velocity observed for the decomposition in tri-*n*-butylamine is of particular interest in comparison with the very marked effect previously observed by P. D. Bartlett and K. Nozaki²² in the decomposition of benzoyl peroxide in amines.

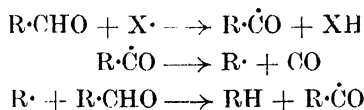
³⁰ *J. Amer. Chem. Soc.*, 1948, **70**, 95.

³¹ J. H. Raley, F. F. Rust, and W. E. Vaughan, *ibid.*, p. 1336.

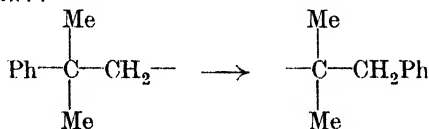
The reaction between *tert.*-butyl peroxide and benzaldehyde has been investigated by F. F. Rust, F. H. Seubold, and W. E. Vaughan,³² who have identified one of the products as *s*-diphenylethyleneglycol dibenzoate (IV). Its formation is readily explained on the basis of the following sequence of reactions :



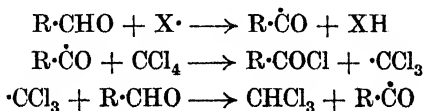
This mechanism is confirmed by the fact that the same glycol dibenzoate is formed from the reaction between (a) benzoyl peroxide and benzaldehyde, and (b) *tert.*-butyl peroxide and benzyl benzoate. Free-radical chain reactions involving aldehydes have also been investigated by S. Winstein and F. H. Seubold,³³ who have demonstrated the occurrence of a peroxide-catalysed reaction of the type :



The reaction with β -phenylisovaleraldehyde and *tert.*-butyl peroxide at 130° gives *tert.*-butylbenzene and *isobutylbenzene*. This reaction provides an interesting confirmation of the partial rearrangement of the neophyl (2-phenyl-2-methylpropyl) radical, previously observed by W. H. Urry and M. S. Kharasch,³⁴ *i.e.* :



At lower temperatures (*e.g.*, 80°) the acyl radical becomes more stable, and with benzoyl peroxide at this temperature most of the aldehyde is recovered unchanged, but when the reaction is conducted in boiling carbon tetrachloride no carbon monoxide is evolved and reaction takes place with the solvent to give chloroform and β -phenylisovaleryl chloride. Since the yields of these products are considerably in excess of the amount of catalyst used, it is considered that a chain reaction takes place which may be represented thus :

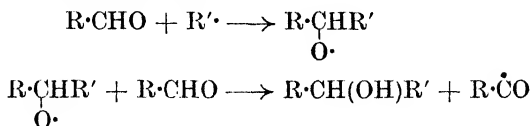


³² *J. Amer. Chem. Soc.*, 1948, **70**, 3258.

³³ *Ibid.*, 1947, **69**, 2916.

³⁴ *Ibid.*, 1944, **66**, 1438.

Later work on the action of *tert.*-butyl peroxide on aliphatic aldehydes has revealed the formation of secondary alcohols which is explained by the addition of the radical to the carbonyl carbon atom followed by removal of a hydrogen atom from the aldehyde : ³⁵



On the other hand, there is evidence which suggests that certain reactions between hydroperoxides and aldehydes are heterolytic in character and involve the anion HO_2^- . ³⁶

Addition Reactions.—An important contribution to the theory of free-radical addition reactions has been made by E. H. Farmer ³⁷ in a review of the occurrence of apolar reactions with olefinic systems in which free radicals or atoms of short life are involved as intermediates. A "radical-addition rule" is put forward for these reactions which may be compared with the Markownikow rule for polar addition reactions. This rule requires that the radical component initiating the reaction must add exclusively to the more hydrogenated ethylenic carbon atom. When compared with polar addition reactions, however, the apolar reactions appear to be less straightforward, since addition represents only one of two possible courses, the second possibility being substitution at an α -methylenic carbon atom. D. H. R. Barton ³⁸ has also discussed the theory of radical-addition reactions, and has pointed out that the characterisation of neutral radicals as electrophilic reagents is unsound. He suggests that free radicals attack preferentially points of high differential electron density (*i.e.*, differential with respect to the symmetrical unsubstituted systems) rather than points of high intrinsic electron density.

The abnormal addition of hydrogen bromide and thiols to unsymmetrical olefinic compounds is known to be effected by the presence of peroxides or by exposure to ultra-violet light. It has now been shown that similar results can readily be achieved in the presence of an organometallic compound, *e.g.*, PbMe_4 , PbEt_4 , SnEt_4 , etc., in the presence of light. ³⁹ It is a well-established fact that the peroxide effect shown with hydrogen bromide is not observed with the addition reactions of hydrogen chloride, but an example of a free-radical addition reaction with hydrogen chloride has now been provided by J. H. Raley, F. F. Rust, and W. E. Vaughan, ⁴⁰ who have investigated the vapour-phase addition of hydrogen chloride to ethylene and

³⁵ F. F. Rust, F. H. Seubold, and W. E. Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 4253.

³⁶ C. A. Bunton, E. S. Halberstadt, A. J. Everett, and G. J. Minkoff, *Nature*, 1948, **161**, 172.

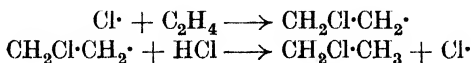
³⁷ *J. Soc. Chem. Ind.*, 1947, **66**, 86.

³⁸ *Nature*, 1948, **162**, 182.

³⁹ T. W. Evans, W. E. Vaughan, and F. F. Rust (Shell Development Company), *B.P.* 567,524.

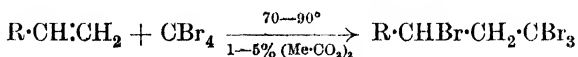
⁴⁰ *J. Amer. Chem. Soc.*, 1948, **70**, 2767.

propylene in the presence of ultra-violet light or *tert.*-butyl peroxide. These reactions are chain processes involving chlorine atoms, and as such are inhibited by oxygen and other substances. The initial homolytic fission of the hydrogen chloride provides a chlorine atom, which then functions as the chain carrier thus :



The reaction with propylene, which proceeds more slowly, gives both *n*- and *iso*-propyl chlorides.

M. S. Kharasch, E. V. Jensen, and W. H. Urry⁴¹ reported in a preliminary announcement in 1946 that carbon tetrabromide reacts additively with ethylenic compounds under the influence of methyl radicals generated from acetyl peroxide, or on irradiation by visible light, thus :

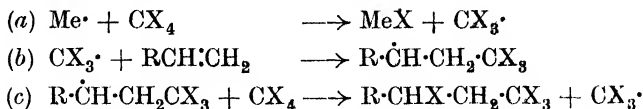


Bromoform was found to react in a similar manner in presence of acetyl peroxide, although this reaction proceeded much more slowly on illumination. In a more detailed study⁴² of the addition reactions of carbon tetrachloride, carbon tetrabromide, chloroform, and bromoform with ethylenic compounds containing a terminal double bond (oct-1-ene, styrene, ethyl acrylate, diallyl, propylene, and ethylene), initiated by either a peroxide or light of appropriate wave-length, it was observed that with the tetrahalides the main product is the simple adduct. Even with styrene, carbon tetrabromide gave the adduct in almost quantitative yield, whereas with carbon tetrachloride the main product was a polymer containing chlorine. In general the reactions with chloroform and bromoform gave appreciably lower yields. When the olefin (1 mol.) was used in the presence of carbon tetrachloride (4 mols.) and carbon tetrabromide (2 mols.), only the carbon tetrabromide adduct was formed. Of these four polyhalogenomethanes the addition reaction takes place most readily and completely with carbon tetrabromide. These reactions are initiated and propagated by the homolytic fission of covalent bonds, and it is to be expected that addition of carbon tetrabromide should proceed more readily than the corresponding reaction with carbon tetrachloride, since the energy of activation for the homolytic fission of the C-Br link is smaller than that for the C-Cl link. When these reactions are initiated by relatively reactive free radicals (such as methyl) the energy of activation of the initial reaction, $\text{Me}\cdot + \text{CX}_4 \longrightarrow \text{MeX} + \text{CX}_3\cdot$, is probably small whether the halogen is chlorine or bromine, but when the reaction is initiated photochemically thus: $\text{CX}_4 + h\nu \longrightarrow \text{CX}_3\cdot + \text{X}\cdot$, a difference between the two halides becomes apparent. Consequently, whereas the addition reaction with carbon tetrabromide can be initiated by visible light, that with carbon

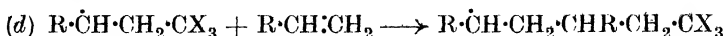
⁴¹ *J. Amer. Chem. Soc.*, 1946, **68**, 154.

⁴² M. S. Kharasch, E. V. Jensen, and W. H. Urry, *ibid.*, 1947, **69**, 1100.

tetrachloride requires light of shorter wave-length. The greater lability of the bromine atom is also evident when free radicals less reactive than methyl are used, and whereas the main course of the chain reaction sequence may be represented as follows :

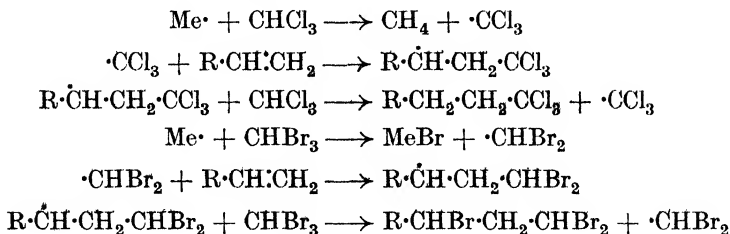


the free radical formed in (b) may itself under suitable conditions react with the olefin thus :



Reaction (d) thus leads to polymerisation whereas reaction (c) gives the simple adduct. When X is Br, reaction (c) predominates. The reactions of ethylene and carbon tetrachloride, in the presence of benzoyl peroxide, have also been studied by R. M. Joyce, W. E. Hanford, and J. Harmon,⁴³ who have confirmed that the initial product is the adduct 1 : 1 : 1 : 3-tetrachloropropane, but that other compounds such as 1 : 1 : 1 : 5-tetrachloropentane and 1 : 1 : 1 : 7-tetrachloro-*n*-heptane may also be formed, depending on the relative concentrations of the reactants. The formation of these compounds of higher molecular weight results from reactions of type (d) followed by chain termination by reaction with carbon tetrachloride. The products from ethylene will always contain an odd number of carbon atoms and will be of the general formula $\text{Cl}[\text{CH}_2\cdot\text{CH}_2]_n\cdot\text{CCl}_3$. Compounds of type $\text{Cl}[\text{CH}_2\cdot\text{CH}_2]_n\cdot\text{Cl}$ and $\text{CCl}_3[\text{CH}_2\cdot\text{CH}_2]_n\cdot\text{CCl}_3$ are not formed.

The addition reactions of chloroform and bromoform follow different courses as represented below :⁴²



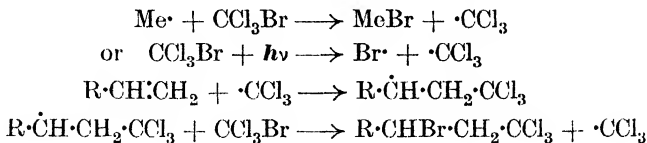
The greater lability of the hydrogen atom in chloroform is in agreement with the observation that in the reaction between benzoyl peroxide and chloroform the product is benzene and not chlorobenzene.¹² The peroxide-catalysed addition of iodoform to an olefin has also been reported.⁴⁴ Limonene and iodoform, in the presence of acetyl peroxide, give a 1 : 2-adduct in 35% yield in which the iodoform has added as $\cdot\text{CHI}_2$ and $\cdot\text{I}$. In this reaction iodoform behaves like bromoform and unlike chloroform.

The addition reactions of trichlorobromomethane resemble those of

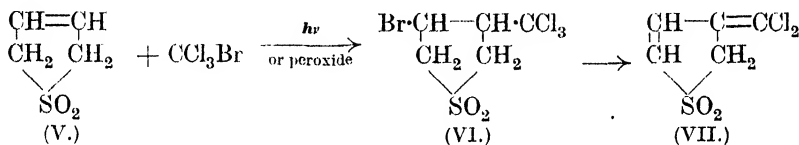
⁴³ *J. Amer. Chem. Soc.*, 1948, **70**, 2529.

⁴⁴ M. Weizmann, S. Israelashvili, A. Halevy, and F. Bergmann, *ibid.*, 1947, **69**, 2509.

carbon tetrabromide rather than those of carbon tetrachloride, with regard to both ease of initiation and propagation, and the nature of the products formed.⁴⁵ These reactions may be represented thus :

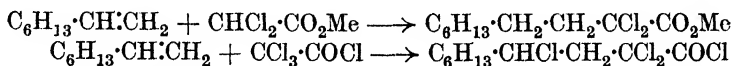


The adduct is usually formed in good yield (70—90%), and the best results are obtained in an atmosphere of nitrogen. M. S. Kharasch, M. Freiman, and W. H. Urry⁴⁶ have also shown that trichlorobromomethane will react with "butadiene sulphone" (V) (2:5-dihydrothiophen 1:1-dioxide) in the presence of a peroxide or when exposed to light to give the addition compound (VI) :



A similar reaction takes place at a slightly higher temperature with carbon tetrachloride and the adduct, as well as the adduct (VI) from trichlorobromomethane, gives (VII) on treatment with two equivalents of alcoholic potassium hydroxide. Addition reactions with olefins in the presence of acetyl peroxide have also been carried out with dichlorobromomethane and with dichlorodibromomethane. The reactions with the former resemble those with bromoform, and the reactions of the latter those with carbon tetrabromide.⁴⁷

Addition reactions of similar character can be carried out between olefins and derivatives of halogenated acids. Oct-1-ene and methyl dichloroacetate or trichloroacetyl chloride react in the presence of acetyl peroxide as follows :⁴⁸



These addition reactions involve the free radicals $\cdot\text{CCl}_2\cdot\text{CO}_2\text{Me}$ and $\cdot\text{CCl}_2\cdot\text{COCl}$. Similar reactions cannot be investigated between free radicals such as $\cdot\text{CH}_2\cdot\text{CO}_2\text{Me}$ and olefins because the olefin is able to compete with the ester for the methyl radical, but since an α -bromine atom is more susceptible to attack by free methyl than α -hydrogen or any hydrogen atom in an olefin it should be possible to use α -bromo-esters to generate free non-halogenated

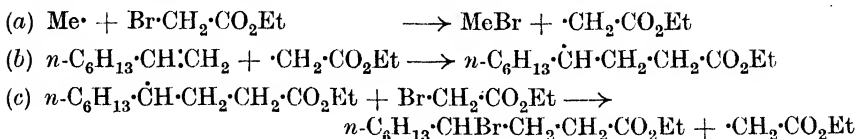
⁴⁵ M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Amer. Chem. Soc.*, 1947, **69**, 1105.

⁴⁶ *J. Org. Chem.*, 1948, **13**, 570.

⁴⁷ M. S. Kharasch, B. M. Kuderna, and W. H. Urry, *ibid.*, p. 895.

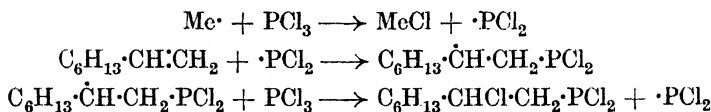
⁴⁸ M. S. Kharasch, W. H. Urry, and E. V. Jensen, *J. Amer. Chem. Soc.*, 1945, **67**, 1626.

ester radicals which might then undergo addition reactions with olefins. Examples of such addition reactions have now been provided.⁴⁰ Thus, oct-1-ene and ethyl bromoacetate in presence of acetyl peroxide give ethyl 3-bromononane-1-carboxylate in good yield as follows :

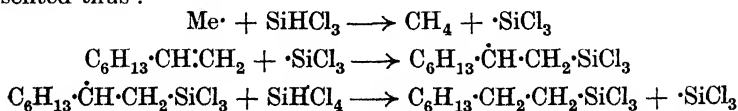


Reactions (b) and (c) constitute a self-sustaining chain reaction provided reaction (b) is rapid. If reaction (b) is not rapid the concentration of the free radical $\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ increases to such an extent that the chain is terminated by dimerisation. It is also necessary for the bromo-ester to react readily by transference of the bromine atom to the free radical produced in reaction (b). Provided these conditions can be fulfilled the reaction is of general application and can be used with straight- and branched-chain mono- and di-carboxylic esters containing an α -bromine atom. The yields are lower with branched-chain esters owing to a greater tendency to undergo dimerisation, and the reaction fails with β -bromo-esters. Addition reactions with α -bromo-esters have been reported with oct-1-ene, propylene, butene, isobutene, styrene, and ethyl acrylate, and the reactions are claimed to constitute a simple one-stage process for the lengthening of a chain by two carbon atoms with the simultaneous introduction of a bromine atom at the γ -position.

It has also been observed⁵⁰ that phosphorus trichloride can be added to double and triple bonds in the presence of peroxides, and this reaction provides a useful method for the preparation of compounds of the type $\text{R}\cdot\text{PCl}_2$. The reaction with oct-1-ene can be represented as follows :



Some higher-boiling products are also formed. A similar reaction between oct-1-ene and trichlorosilane has also been reported.⁵¹ This reaction, which can be initiated with a peroxide or by means of ultra-violet light, provides a new method for the preparation of organosilicon compounds and can be represented thus :



Trichlorosilane thus reacts in the same manner as does chloroform in that

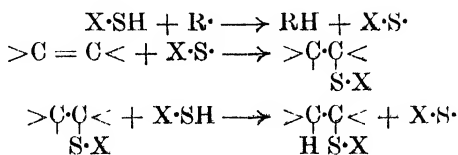
⁴⁰ M. S. Kharasch, P. S. Skell, and F. Fisher, *J. Amer. Chem. Soc.*, 1948, **70**, 1055.

⁵⁰ M. S. Kharasch, E. V. Jensen, and W. H. Urry, *ibid.*, 1945, **67**, 1864.

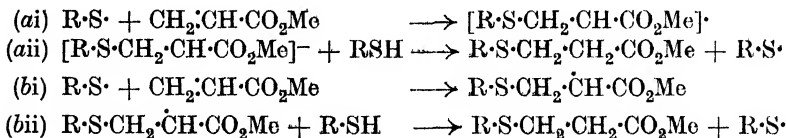
⁵¹ L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *ibid.*, 1947, **69**, 188.

both compounds lose a hydrogen atom to the free methyl radical, whereas with bromoform and iodoform one of the carbon-halogen bonds is severed.

The addition of thio-compounds to olefins under peroxidic conditions has been investigated by J. I. Cunneen.⁵² It has been shown that under these conditions *cyclohexene* and 1-methyl*cyclohexene* add the fragments formed by the scission of the SH bond in thioglycollic acid, thiophenol, and *isopentanethiol*. In the reactions with 1-methyl*cyclohexene* the addition is contrary to the Markownikow rule. Similar addition reactions with thiolacetic acid and with mono-, di-, and tri-chlorothiolacetic acids⁵³ proceed very much more readily, and a parallelism is noted between the ease of thiol addition and the ease of proton removal from the -SH group as measured by acidity. The thio-acid adducts of rubber are of some technological interest as oil-resistant rubber-like materials. These reactions can be represented as follows :



in which R is an alkyl or aryl radical and X is $\text{CH}_2\cdot\text{CO}_2\text{H}$, Ph, $\text{CH}_2\cdot\text{CO}$, $\text{CH}_2\text{Cl}\cdot\text{CO}$, $\text{CHCl}_2\cdot\text{CO}$, or $\text{CCl}_3\cdot\text{CO}$. An investigation of the addition of thiols to methyl acrylate⁵⁴ has shown that the reaction only proceeds in the presence of *either* a strong base or a peroxide (or ultra-violet light), and that in *both* cases the same addition compound is formed. These two reactions can be represented thus :



The intermediate ion or radical, formed in (ai) or (bi), is that of the lowest energy content (*i.e.*, secondary). This result is one of special interest, since hitherto it was not known whether both the ionic and the atomic mechanisms could operate in the addition of hydrogen bromide to $\alpha\beta$ -double bonds. No reversal of the addition was observed under peroxidic conditions, and the product from methyl acrylate was invariably methyl β -bromopropionate. It now seems highly probable that both mechanisms can operate under the appropriate experimental conditions, but give rise to the same product.

Addition reactions of maleic esters in the presence of benzoyl peroxide have been reported by C. S. Marvel, E. J. Prill, and D. F. DeTar.⁵⁵ The

⁵² *J.*, 1947, 36.

⁵³ J. I. Cunneen, *J.*, 1947, 134.

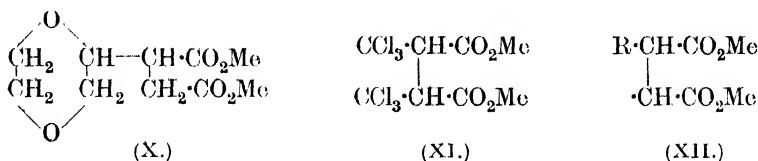
⁵⁴ M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, 1948, 13, 97.

⁵⁵ *J. Amer. Chem. Soc.*, 1947, 69, 52.

products from the reaction between methyl maleate (2 mols.) and benzoyl peroxide (1 mol.) at 55° are methyl phenylsuccinate (5%), two esters of empirical formula $C_{18}H_{20}O_8$ (25%), and a non-volatile residue (30—40%), unchanged methyl maleate (about 15%) being recovered. The two esters are regarded as stereoisomeric forms of either (VIII) or (IX) :



When dioxan or carbon tetrachloride is used as solvent in the above reaction the products contain compounds such as (X) and (XI) formed by free-radical attack on the solvent molecules :



The production of these compounds results from the intermediate formation of phenyl, dioxanyl, and trichloromethyl radicals, the last two being derived from the reaction of the solvent molecules with a free radical from the peroxide. These three radicals R can each add to the maleic ester to give a new radical (XII). A subsequent chain transfer with the solvent gives (X) or (XI). The free radical (XII) may also react with a second molecule of the maleic ester, and, when R is Ph, this gives rise to (VIII) or (IX) by an internal chain-transfer reaction. The reactions of diazonium salts with citraconic, mesaconic, maleic, and acrylic acids have also been studied,^{56, 57} and the results are in general agreement with those of earlier workers.⁵⁸

Reactions of Halogen Atoms.—A. Robertson and W. A. Waters⁵⁹ have provided experimental evidence for homolytic bond fission in many compounds containing a so-called “positive” halogen atom, which is revealed by the capacity to function as catalysts for the autoxidation of tetrahydronaphthalene. *N*-Chloroamides, which liberate iodine instantaneously from hydrogen iodide, are immediate catalysts, whereas less active compounds function only after an induction period. The most generally effective compound for atomic bromination continues to be *N*-bromosuccinimide,⁶⁰ and numerous examples have been provided during the past four years of its uses for the bromination of α -methylene groups and aromatic side-chains. It has had many useful applications in the steroid field.⁶¹ A comprehensive review of the reactions and uses of *N*-bromosuccinimide has been published

⁵⁶ D. R. Dhingra and K. B. L. Mathur, *J. Indian Chem. Soc.*, 1947, **24**, 123.

⁵⁷ J. Rai and K. B. L. Mathur, *ibid.*, pp. 383, 413.

⁵⁸ See ref. 1, p. 183.

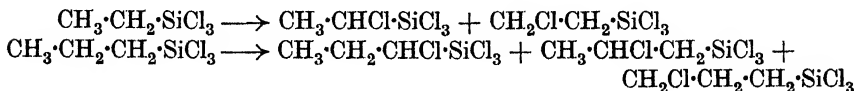
⁵⁹ *J.*, 1947, 492.

⁶⁰ See ref. 1, p. 191.

⁶¹ C. W. Shoppee, *Ann. Reports*, 1947, **44**, 184.

by C. Djerassi.⁶² Confirmation of the homolytic mechanism for the reactions of *N*-bromosuccinimide with α -methylenic groups and aromatic side-chains has been provided by H. Schmid and P. Karrer,⁶³ who have shown that the addition of benzoyl peroxide (5–10 mols. %) results in faster and smoother reactions. These results have been confirmed by E. R. Buchman and D. R. Howton,⁶⁴ and many other workers have adopted the method. The accelerating influence of ultra-violet light has also been demonstrated.⁶⁵ H. Schmid⁶⁶ has shown that some inorganic salts (*e.g.*, AlCl_3 , ZnCl_2 , FeCl_3) and concentrated sulphuric acid can act as catalysts for certain bromination reactions with *N*-bromosuccinimide, but molecular equivalents are required and the resulting reactions obviously proceed by a polar mechanism since under these conditions benzene is brominated and toluene undergoes almost complete nuclear substitution. It is thus established that *N*-bromosuccinimide can function as a brominating agent by two different mechanisms. Further supporting evidence for the homolytic mechanism has been provided by D. R. Howton,⁶⁷ who showed that when benzene was used as solvent for the bromination of cyclohexene with *N*-bromosuccinimide the product contained a small quantity of *N*-phenylsuccinimide. A similar observation had been made earlier with acridine,^{63, 68} and this represents a new type of amidation reaction, which recalls the many known substitution reactions of free radicals with aromatic nuclei. R. A. Barnes⁶⁹ has shown that *N*-bromosuccinimide can be used in certain cases as a low-temperature dehydrogenating agent, but with decalin a tetrabromide is formed by way of a free-radical intermediate.

Examples of the use of sulphuryl chloride as a peroxide-catalysed chlorinating agent have been previously reported.⁷⁰ The usefulness of this procedure has been further extended to its application to the chlorination of silicon compounds. L. H. Sommer, F. C. Whitmore, and their co-workers^{71, 72} have shown that sulphuryl chloride in the presence of benzoyl peroxide is an excellent chlorinating agent for alkyltrichlorosilanes other than the methyl derivative, and provides a method which is superior to photochemical chlorination. Under these conditions ethyltrichlorosilane and *n*-propyltrichlorosilane react as follows :



⁶² *Chem. Reviews*, 1948, **43**, 271.

⁶³ *Helv. Chim. Acta*, 1946, **29**, 573.

⁶⁴ *J. Amer. Chem. Soc.*, 1948, **70**, 2517.

⁶⁵ C. Meystre, L. Ehmann, R. Neher, and K. Miescher, *Helv. Chim. Acta*, 1945, **28**, 1252.

⁶⁶ *Ibid.*, 1946, **29**, 1144.

⁶⁷ *J. Amer. Chem. Soc.*, 1947, **69**, 2060; see also ref. 64.

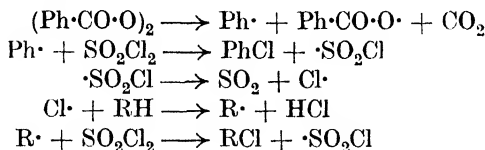
⁶⁸ H. Schmid and W. E. Leutenegger, *Helv. Chim. Acta*, 1947, **30**, 1965.

⁶⁹ *J. Amer. Chem. Soc.*, 1948, **70**, 145. ⁷⁰ Ref. 1, p. 186.

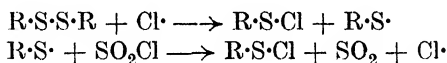
⁷¹ L. H. Sommer and F. C. Whitmore, *J. Amer. Chem. Soc.*, 1946, **68**, 485.

⁷² L. H. Sommer, E. Dorfman, G. M. Goldberg, and F. C. Whitmore, *ibid.*, p. 488.

Trimethylchlorosilane and *tert.*-butyl chloride can also be chlorinated with sulphuryl chloride in the presence of benzoyl peroxide,⁷³ and the same method has been applied to ethylpentachlorobenzene to give 1-chloro-2-pentachlorophenylethane, *i.e.*, β -chlorination,⁷⁴ which compound is also formed on photochlorination. These reactions proceed by a free-radical chain mechanism which can be generalised as follows :



On the other hand, bromination of ethylpentachlorobenzene, which is also photocatalytic, gives 1-bromo-1-pentachlorophenylethane, *i.e.*, α -bromination.⁷⁵ An interesting observation has been made by A. J. Farnworth and J. B. Speakman,⁷⁶ who found that when wool, freed from adsorbed soap and residual oil, is treated with sulphuryl chloride, the disulphide bond fission in the fibre surfaces is less effective than when untreated wool is used. This effect has been shown to be due to the presence of oleic acid (and concomitant peroxides) in the untreated wool, which promotes the formation on the fibre surfaces of atomic chlorine, which is the effective agent in bringing out the homolytic fission of the disulphide bond :



The presence of stearic acid produces no such effect. M. S. Kharasch and A. F. Zavist⁷⁷ have shown that sulphuryl chloride in the presence of a peroxide can also be used for the preparation of sulphonyl chlorides. The product from oct-1-ene has the empirical formula $\text{C}_{16}\text{H}_{32}\text{O}_2\text{Cl}_2\text{S}$ (*i.e.*, $2\text{C}_8\text{H}_{16} + \text{SO}_2\text{Cl}_2$). The exact nature of this reaction is still somewhat obscure, and its further investigation is awaited with interest.

Miscellaneous Reactions.—Further examples have been provided of the use of the Gomberg reaction and of the closely related nitrosoacylarylamine method for effecting the union of aryl nuclei,^{78, 79} and nitrosoacylarylamines have been employed as catalysts for the polymerisation of styrene, methyl methacrylate, and acrylonitrile.⁸⁰ The use of certain aromatic diazo-compounds and triazens for the initiation of polymerisation when it is desired to reduce to a minimum the effects of oxidation and cross-linking

⁷³ J. J. McBride and H. C. Beachell, *J. Amer. Chem. Soc.*, 1948, **70**, 2532.

⁷⁴ S. D. Ross, M. Markarian, and M. Nazzewski, *ibid.*, 1947, **69**, 1914.

⁷⁵ *Idem*, *ibid.*, p. 2468.

⁷⁶ *Nature*, 1948, **161**, 850.

⁷⁷ *J. Amer. Chem. Soc.*, 1948, **70**, 3526.

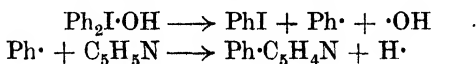
⁷⁸ C. C. Price, H. R. Snyder, and E. M. Van Heyningen, *ibid.*, 1946, **68**, 2589.

⁷⁹ W. J. Dunstan and G. K. Hughes, *J. Proc. Roy. Soc. New South Wales*, 1946, **80**, 77.

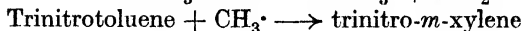
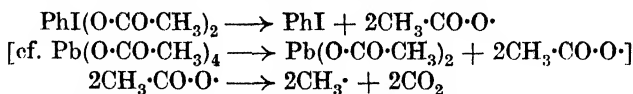
⁸⁰ D. H. Hey and G. S. Misra, *Faraday Society Discussion*, 1947, **2**, 279.

has also been recommended.⁸¹ Benzyl hyponitrite, reported to be an effective catalyst for the polymerisation of methyl methacrylate, acts by homolytic fission to give nitrogen and two benzyloxy-radicals.⁸² A. W. Johnson⁸³ has shown that 2-arylfurans are the main products formed in the reactions between aqueous diazonium salts in the presence of alkali, or nitrosoacetylarylamines, and furan, and in the only reaction studied in detail a small yield of the isomeric 3-arylfuran was also isolated. These results confirm the view that in the nuclear substitution of aromatic (and heterocyclic) compounds by free radicals the original conception of an approximately uniform rate of substitution at all orientation positions is almost certainly too crude, and W. A. Waters⁸⁴ has already drawn attention to the significance of the transition state and of semi-quinonoid structures in such reactions. The observed predominance of substitution at the *ortho*-position in anisole⁷⁹ is particularly significant.

R. B. Sandin and R. K. Brown⁸⁵ have made the interesting observation that when diphenyliodonium chloride decomposes in the presence of pyridine and aqueous sodium hydroxide a mixture of the three isomeric phenylpyridines is formed, suggesting that in this reaction the iodonium hydroxide breaks down homolytically to give free phenyl radicals, which then react with pyridine at the α -, β -, and γ -positions, thus :



In 1939⁸⁶ it had been shown that aryliodosoacetates oxidise unsaturated compounds in much the same manner as lead tetra-acetate, and R. B. Sandin and W. B. McCormack⁸⁷ have now shown that, like lead tetra-acetate, phenyl iodosoacetate can function as a methylating agent for aromatic nitro-compounds. As with lead tetra-acetate, acetate radicals are involved which yield carbon dioxide and methyl radicals, thus :



It is generally understood that the decomposition of an organic molecule by the homolytic fission of a covalent bond is a process most likely to be encountered in typical non-polar solvents of low dielectric constant, but K. H. Saunders and W. A. Waters⁸⁸ have discussed the possibility of the formation of free aryl radicals from aromatic diazo-compounds in aqueous solution under neutral or mild alkaline conditions. These extensions of homolytic processes to reactions in aqueous media have been criticised by

⁸¹ B. S. Garvey and B. F. Goodrich Co., U.S.P. 2,376,963; W. F. Semon and B. F. Goodrich Co., U.S.P. 2,376,014, 2,376,015.

⁸² I. Harris, I. Marshall, and K. B. Jarrett, *Nature*, 1947, **159**, 843.

⁸³ *J.*, 1946, 895.

⁸⁴ *J.*, 1948, 727.

⁸⁵ *J. Amer. Chem. Soc.*, 1947, **69**, 2253.

⁸⁶ R. Griegee and H. Beucker, *Annalen*, 1939, **541**, 218.

⁸⁷ *J. Amer. Chem. Soc.*, 1945, **67**, 2051.

⁸⁸ *J.*, 1946, 1154.

H. H. Hodgson, who has proposed a theory in which free radicals are not involved in either aqueous or non-aqueous media.^{88, 90} In the absence of any new experimental evidence these views, in so far as they apply to reactions in non-aqueous solutions, have been rejected by D. H. Hey and W. A. Waters,^{91, 92} since they raise insuperable difficulties and cannot easily be reconciled with many of the observations from the accumulation of established experimental facts.

R. B. Thompson and J. A. Chenicek⁹³ have observed that although acetic acid, which is frequently used as a solvent for oxidation reactions with selenium dioxide, is normally regarded as inert at the temperature of its boiling point, at higher temperatures (200° for 12 hours) it is attacked by the oxidising agent with formation of succinic acid in small yield. The succinic acid is considered to be derived by dimerisation of two $\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ radicals, as in Kharasch's method for the preparation of succinic acid from acetic acid using methyl radicals derived from acetyl peroxide.⁷ A study of the mechanism of oxidation processes with chromic anhydride has been made by W. A. Waters and R. Slack,^{94, 95} who have shown that in many cases oxygen is absorbed during the reaction, from which it is concluded that an initial dehydrogenation process is involved whereby free organic radicals are generated. A. Robertson and W. A. Waters^{96, 97} have also studied the autoxidation of tetralin, which is shown to proceed through the hydroperoxide and a free-radical mechanism, and a similar explanation has been provided for the oxidation of ethylbenzene by air.⁹⁸

The possibility of the formation of free radicals by means of ionising radiations has been investigated by G. Stein and J. Weiss,⁹⁹ who have shown that when a suspension of benzene in oxygen-free water is irradiated with X-rays traces of phenol and diphenyl are formed, and in similar manner benzoic acid gives hydroxybenzoic acids including salicylic acid. When a γ -ray source was used benzene gave, in addition, catechol. These results, which depend on the pH of the solutions used, are interpreted by the intervention of hydroxyl radicals. F. S. Dainton¹⁰⁰ had previously shown that dilute aqueous solutions of acrylonitrile underwent polymerisation under the influence of X-rays and γ -rays, and this was attributed to the free hydroxyl radical which had already been shown to be a typical polymerisation catalyst.¹⁰¹ The participation of hydroxyl radicals in the oxidation of alcohols with Fenton's reagent has been demonstrated by J. H. Merz and W. A. Waters.¹⁰²

⁸⁸ *J.*, 1948, 348.

⁹⁰ *J. Soc. Dyers Col.*, 1948, **64**, 99.

⁹¹ *J.*, 1948, 882.

⁹² *J. Soc. Dyers Col.*, 1948, **64**, 359.

⁹³ *J. Amer. Chem. Soc.*, 1947, **69**, 2563.

⁹⁴ W. A. Waters, *J.*, 1946, 1151.

⁹⁵ R. Slack and W. A. Waters, *J.*, 1948, 1666.

⁹⁶ *Trans. Faraday Soc.*, 1946, **42**, 201.

⁹⁷ *J.*, 1948, 1574, 1578, 1585.

⁹⁸ W. S. Emerson, J. W. Heyd, V. E. Lucas, W. B. Cook, W. I. Lyness, and J. K. Stevenson, *J. Amer. Chem. Soc.*, 1948, **70**, 3764.

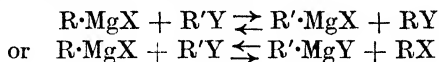
⁹⁹ *Nature*, 1948, **161**, 650.

¹⁰⁰ *Ibid.*, 1947, **160**, 268.

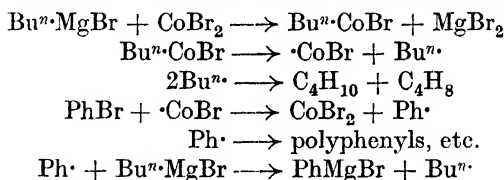
¹⁰¹ J. H. Baxendale, M. G. Evans, and G. S. Park, *Trans. Faraday Soc.*, 1946, **42**, 155.

¹⁰² *Faraday Soc. Discussion*, 1947, **2**, 179.

The work of M. S. Kharasch and his co-workers on the reactions of Grignard reagents in the presence of certain metallic halides was reviewed in 1944.¹⁰³ Since that time further contributions to this subject have been made from the same laboratories. M. S. Kharasch and C. F. Fuchs¹⁰⁴ have shown that equilibria of the type :



may occur in the presence of a catalytic quantity of a cobaltous halide, and the existence of the interchange is revealed by treatment of the mixture with carbon dioxide, which gives a mixture of carboxylic acids. A small number of examples are known in which the interchange occurs even in the absence of a metallic halide (*e.g.*, ethylmagnesium bromide and cyclohexyl bromide), but these are exceptions to the general rule. The mechanism suggested for the interchange of radicals is given provisionally as follows for the reaction between *n*-butylmagnesium bromide and bromobenzene :



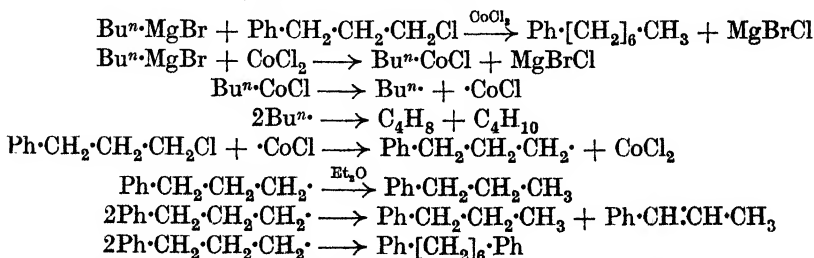
M. S. Kharasch, F. L. Lambert, and W. H. Urry¹⁰⁵ have reported an investigation on the effect of metallic halides on the reactions of Grignard reagents with 3-chloro-1-phenylpropane, cinnamyl chloride, and phenylethynyl bromide. In the presence of cobaltous chloride, 3-chloro-1-phenylpropane reacts with ethylmagnesium bromide and with *n*-butylmagnesium bromide as follows :

| Products. | With Me·MgBr (%). | With Bu ⁿ ·MgBr (%). |
|--|-------------------|---------------------------------|
| Ph·CH ₂ ·CH ₂ ·CH ₃ | 17.5 | 46 |
| Ph·CH=CH·CH ₃ | 39.0 | 24 |
| Gases | 89.4 * | 82 † |
| Higher-boiling compounds | 37.2 | 15 † |

* CH₄ 90%; C₂H₄ 5%; C₂H₆ 5%. † C₄H₁₀ 50%; C₄H₈ 50%.

‡ Mainly *n*-heptylbenzene and 1 : 6-diphenylhexane.

No reaction takes place in the absence of the cobalt halide. The course of these reactions can be represented as follows :

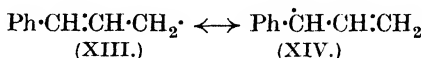


¹⁰³ See ref. 1, p. 195.

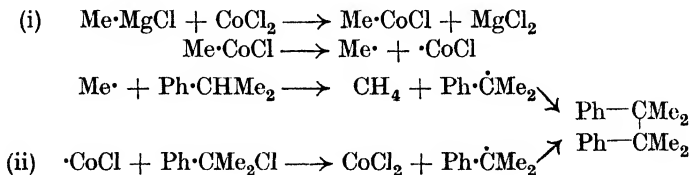
¹⁰⁴ *J. Org. Chem.*, 1945, 10, 292.

¹⁰⁵ *Ibid.*, p. 298.

In the corresponding reaction with methylmagnesium bromide the more reactive methyl radical reacts with the solvent (ether) and also with 3-chloro-1-phenylpropane to give more β -methylstyrene, more higher-boiling products, and a marked difference in the composition of the gaseous products. With cinnamyl chloride in the presence of cobaltous chloride, methylmagnesium bromide gives 1-phenylbut-1-ene (12%), 1:6-diphenylhexa-1:5-diene (30%), and 1:4-diphenylhexa-1:5-diene (40%), whereas in the absence of the metallic halide the three compounds are formed in yields of 89%, 1%, and 5% respectively. The radical formed can be represented as a resonance hybrid of the cinnamyl (XIII) and phenylvinylmethyl (XIV) forms :



and would be expected to undergo dimerisation to give 1:6-, 1:4-, and 3:4-diphenylhexa-1:5-diene, but only the first two compounds were identified in the product. This result is in agreement with the later work of H. P. Koch previously reported,¹⁹ who obtained the phenylvinylmethyl radical by the action of acetyl peroxide on allylbenzene. Methylmagnesium bromide reacts with phenylethynyl bromide to give phenylethynylmagnesium bromide and methyl bromide, but in presence of cobaltous chloride 1-phenyl-2-methylacetylene is formed in 62% yield. The use of methyl radicals to bring about the formation and subsequent dimerisation of other radicals has been further investigated by M. S. Kharasch and W. H. Urry.¹⁰⁶ In a mixture of methylmagnesium bromide, methyl bromide, cobaltous chloride, and *isopropylbenzene*, the free methyl radicals attack predominantly the solvent (ether), and the yield of 2:3-diphenyl-2:3-dimethylbutane is small, but with removal of the ether and a higher temperature the yield of the dimeride is increased. The same dimeride results from the action of a cobalt sub-halide on α -chloro*isopropylbenzene*, and the two processes can be summarised thus :



The formation of 2:3-diphenyl-2:3-dimethylbutane from *isopropylbenzene* in other free-radical processes has been reported above.^{10, 29} L. H. P. Weldon and C. L. Wilson¹⁰⁷ have made the interesting observation that pure *p*-dideuterobenzene cannot be prepared from *p*-dibromobenzene by the reaction of the double Grignard reagent with deuterium oxide. Under these conditions the product contained some monodeuterobenzene. On the other hand, if the reaction was carried out in two stages, *via p*-bromomonodeuterobenzene, pure *p*-dideuterobenzene was obtained.

108 *J. Org. Chem.*, 1948, 13, 101.
REF.—VOL. XLV.

¹⁰⁷ *J.*, 1946, 235.

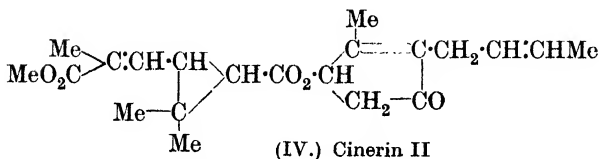
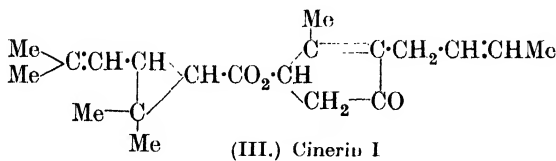
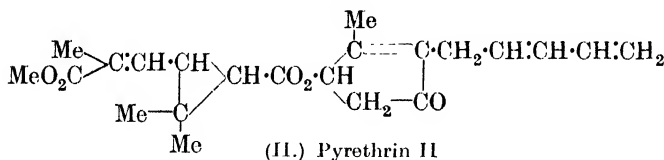
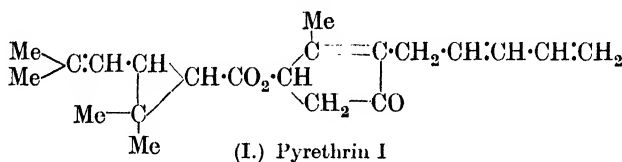
An explanation of these results is found in the suggestion that the di-magnesium bromide gives rise to a free-radical intermediate which acquires ordinary hydrogen from the solvent ether.

D. H. H.

4. TERPENES.

Monoterpenes.

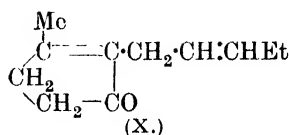
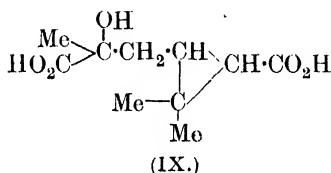
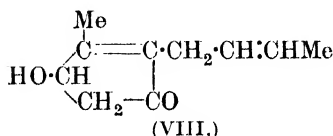
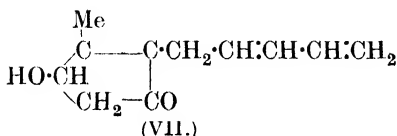
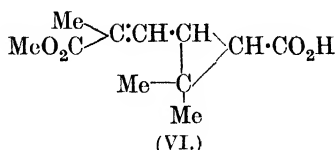
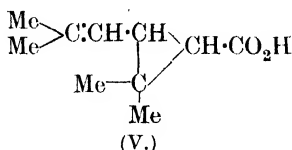
The first clear and comprehensive account of the nature of the insecticidal constituents of pyrethrum flowers (*Chrysanthemum cinerariifolium*) was given in an outstanding series of papers by H. Staudinger and L. Ruzicka¹ published just twenty-five years ago.* While their broad conclusions have not been disproved, there have been important changes in detail. In order to keep this report within reasonable compass it is proposed to state the currently accepted constitutions of these insecticidal substances and to review the evidence for the more important features of these structures, particularly where these differ from those deduced by H. Staudinger and L. Ruzicka. These formulæ are :



¹ *Helv. Chim. Acta*, 1924, 7, 177, 201, 212, 236, 245, 377, 390, 406, 442, 448; also *Ann. Acad. Sci. Fennicae*, 1927, A, 29, No. 17.

* This topic was last reviewed in *Ann. Reports* in 1923 (vol. 20, p. 98), immediately before the publication of Staudinger and Ruzicka's work, and that review dealt with some early Japanese work which the present Reporter considers erroneous. Neither Staudinger and Ruzicka's nor subsequent work has therefore been reported.

These four structures have several features in common. They are all esters, of which the acidic components are the monoterpenic acids, chrysanthemum-monocarboxylic acid (V), and the monomethyl ester of chrysanthemumdicarboxylic acid (VI). The alcoholic components are the cyclic keto-alcohols, pyrethrolone (VII) and cinerolone (VIII).



As far as the Reporter is aware the chrysanthemum acids are unique among natural products in containing an unfused *cyclopropane* ring. This suggests a possible origin in the fission of suitable dicyclic monoterpenes containing the fused *cyclopropane* ring. In fact J. L. Simonsen and M. G. Rau² obtained the *laevo-trans*-hydroxydicarboxylic acid (IX), by oxidative degradation of car-3-ene, which if dehydrated could give the correct stereoisomer of chrysanthemumdicarboxylic acid. If this were the origin of the chrysanthemum acids, then the presence of a carene or related terpene in the essential oil of pyrethrum flowers might be expected. However, R. P. Merritt and T. F. West³ examined this oil without discovering the presence of any terpenes. Likewise pyrethrolone and cinerolone have few counterparts in Nature, and the closest is probably jasmone (X).

That the insecticidal constituent of Japanese pyrethrum is an ester, whose toxicity is destroyed by hydrolysis, was demonstrated by J. Fujitani⁴ and by R. Yamamoto.⁵ Meanwhile H. Staudinger and L. Ruzicka⁶ working with Dalmatian pyrethrum (their work was carried out during 1910—1916, but not published until 1924) isolated a similar fraction, and made the important discovery that this fraction gave a crystalline though heterogeneous semicarbazone, from which acid hydrolysis regenerated a

² *J.*, 1923, **123**, 549.

³ *J. Soc. Chem. Ind.*, 1938, **57**, 321r.

⁴ *Arch. exp. Path. Pharm.*, 1909, **61**, 47.

⁵ *J. Tokyo Chem. Soc.*, 1919, **40**, 126; *J. Chem. Soc. Japan*, 1923, **44**, 311.

⁶ *Helv. Chim. Acta*, 1924, **7**, 177.

toxic keto-ester. Saponification of this semicarbazone with cold sodium methoxide yielded a single keto-alcohol semicarbazone and three acids, chrysanthemum-monocarboxylic acid, chrysanthemumdicarboxylic acid, and the monomethyl ester of the latter. Staudinger and Ruzicka therefore concluded that the insecticidal action of pyrethrum is due to the presence of two esters, pyrethrin I and pyrethrin II, derived from esterification of pyrethrolone with chrysanthemum-monocarboxylic acid and the monomethyl ester of chrysanthemumdicarboxylic acid, respectively. The binary nature of the "pyrethrins" was accepted for twenty years, until F. B. LaForge and W. F. Barthel⁷ subjected crude pyrethrolone to fractionation by distillation of the acetate and crystallisation of the acetate semicarbazone and obtained no less than five distinct semicarbazones, to which T. F. West⁸ has added a sixth. These were shown to be derived from the *dextro*- and racemic forms of three keto-alcohols, for the first two of which the name pyrethrolone was retained, while for the third the name cinerolone was introduced, the esters of cinerolone with the chrysanthemum acids being cinerins. The racemic pyrethrolones are almost certainly artefacts of the isolation procedure, for West⁸ isolated only the optically active alcohols by direct fractional distillation of crude pyrethrolone. The pyrethrolone giving the higher-melting semicarbazone is the major component. Nevertheless if each of these three alcohols is esterified with the two acids, no less than six "pyrethrins" are possible, two being represented by formula (I), two by (II), one by (III), and one by (IV). Whether all six are present in varying proportions in pyrethrum extract is not known, for there has been no direct study of the heterogeneity of "pyrethrin I" and "pyrethrin II." The terms pyrethrin I and pyrethrin II are now often used to describe all naturally occurring esters derived from the chrysanthemum-mono- and -dicarboxylic acids, respectively, with cyclic keto-alcohols of the pyrethrolone type. When these terms are used in this wider sense, they will be printed within quotation marks.

The picture is still further complicated, for H. L. Haller and F. B. LaForge⁹ have shown that crude "pyrethrin I" contains nearly 10% of "pyrethrolone" esterified with palmitic and linoleic acids. Whether these esters are toxic is not known.

The disclosure of the heterogeneity of "pyrethrolone" has made much of the degradative work carried out before 1945, particularly that directed towards elucidating the positions of the double bonds in the side-chain of pyrethrolone, of uncertain value. It is not proposed to describe this work in detail, nor the several structures put forward in attempts to accommodate conflicting data.

Extracts containing 25—30% of "pyrethrins" are available commercially, or are readily prepared on a laboratory scale by solvent extraction of the ground flowers. Light petroleum is preferred as extracting less extraneous

⁷ *J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106.

⁸ *J.*, 1946, 463.

⁹ *J. Org. Chem.*, 1937, **2**, 56; F. Acree and F. B. LaForge, *ibid.*, p. 308.

material.^{6, 10} Incorporation of decolorising carbon with the ground flowers,¹¹ or percolating the extracts through a column of activated carbon,¹² has been shown to remove accompanying pigments. Refrigerating solutions in absolute or aqueous methanol⁶ or aqueous acetic acid¹³ precipitates resin and fat. Extracts of fresh flowers contain little free acids, but where these are present, as in extracts of aged flowers, they can be removed, though with difficulty due to emulsification, by agitation of a cooled light petroleum⁶ or aniline¹³ solution with aqueous potassium carbonate. Such partly purified extracts yield the mixed semicarbazones of "pyrethrins I and II," which have not been satisfactorily separated by fractional crystallisation.⁶ Semicarbazide hydrochloride in aqueous pyridine has been shown to give a higher yield of semicarbazones than does semicarbazide hydrochloride in aqueous sodium acetate.¹⁴ The mixed semicarbazones are hydrolysed by cold sodium methoxide to "pyrethrolone" semicarbazone, which has been further hydrolysed by cold aqueous potassium hydrogen sulphate in benzene¹⁵ or ether¹⁶ to "pyrethrolone"; other methods or higher temperatures lead to partial or complete racemisation.

Further concentration of the "pyrethrins" has been effected by repeated liquid-liquid partitions. As "pyrethrin II" concentrates in the more polar layer, partition between light petroleum and aqueous methanol¹⁷ or light petroleum and aqueous acetic acid¹³ has yielded concentrates containing 80—90% of "pyrethrin II," which readily give an apparently pure semicarbazone.^{14, 18} "Pyrethrin II" of 100% purity has been regenerated from this semicarbazone by hydrolysis with hot aqueous oxalic acid.¹⁸ These preparations of "pyrethrin II" appear to have been substantially homogeneous and derived from pyrethrolone, for hydrolysis of the semicarbazone gave nearly pure pyrethrolone semicarbazone. The "pyrethrin I" concentrates obtained were much poorer (40—70% of "pyrethrin I"),¹³ and contained "pyrethrin II," which may well be largely cinerin II, the palmitic and linoleic esters of "pyrethrolone," and non-toxic impurities. The "pyrethrin I" semicarbazone prepared from these concentrates is not pure¹⁴ and regenerates a concentrate containing, at the best, 65% of "pyrethrin I."¹⁸ While it is likely that improved results could be obtained by use of the Craig distribution technique, a noteworthy advance has been

¹⁰ W. A. Gersdorff and W. M. Davidson, *Ind. Eng. Chem.*, 1929, **21**, 1251; R. Neu, *Seifensieder Ztg.*, 1932, **29**, 790.

¹¹ J. T. Martin and C. Potter, *Chem. and Ind.*, 1937, **56**, 119; J. T. Martin, *J. Agr. Sci.*, 1938, **28**, 456; 1941, **31**, 178.

¹² W. F. Barthel, H. L. Haller, and F. B. LaForge, *Soap*, 1944, **20**, No. 7, 121; W. F. Barthel and H. L. Haller, *Ind. Eng. Chem. Anal.*, 1945, **17**, 529.

¹³ F. B. LaForge and H. L. Haller, *J. Amer. Chem. Soc.*, 1935, **57**, 1893.

¹⁴ *Idem*, *J. Org. Chem.*, 1936, **1**, 38.

¹⁵ H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 212.

¹⁶ F. B. LaForge and H. L. Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1777.

¹⁷ F. Wilcoxon and A. Hartzell, *Contrib. Boyce Thompson Inst.*, 1933, **5**, 115; J. Ripert and O. Gaudin, *Compt. rend.*, 1935, **200**, 2219.

¹⁸ A. E. Gillam and T. F. West, *J.*, 1942, 671.

made by W. F. Barthel, H. L. Haller, and F. B. LaForge¹² who showed that direct extraction of a light petroleum or kerosene solution with nitromethane, followed by passage through a column of activated carbon, yields a concentrate of 90—100% of "pyrethrins." No attempt has been described of using such a concentrate to obtain pure pyrethrin I or to prove the existence of the cinerins by isolation of cinerin I or cinerin II.

Distillation of the "pyrethrins" has not so far proved very successful for purification. Both Staudinger and Ruzicka⁶ and Haller and LaForge found that recovery was low, there being a forerun and much undistillable residue. The latter distilled an 80% "pyrethrin II" concentrate and obtained a product analysing as 100% "pyrethrin II";¹³ nevertheless this failed to give the characteristic semicarbazone readily obtained from the undistilled material.¹⁴ "Pyrethrin I" similarly undergoes some transformation on distillation.¹⁴ These changes have not yet been fully elucidated. Pyrethrins derived from pyrethrolone contain both diene and dienophile groups and would be expected to undergo ready thermal polymerisation of the Diels-Alder type. Consistent with this is the observation of F. B. LaForge and W. F. Barthel¹⁹ that pyrethrolone is less stable to prolonged heating than is cinerolone. M. Elliott and S. H. Harper²⁰ have observed, while distilling synthetic analogues of "pyrethrin I" containing butyl and amyl side-chains, that the forerun contains free acid, evidently formed by thermal elimination and consequent olefin formation. The resulting cyclopentadienone may account for the yellow colour of the distillate, and would readily polymerise.

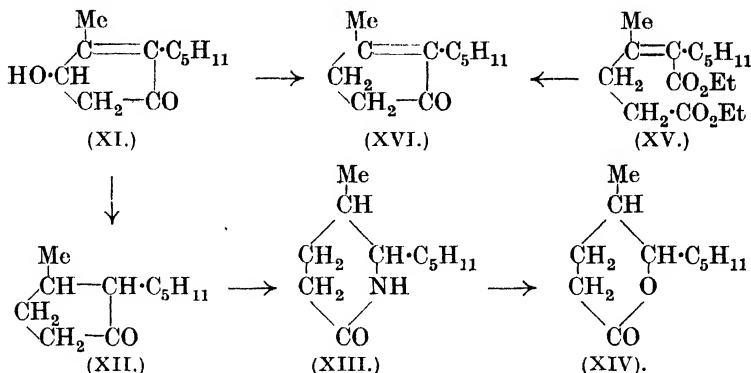
Pyrethrolone, pyrethrolone acetate, and pyrethrolone semicarbazone are hydrogenated with ease to the tetrahydro-stage,^{14, 15} but with difficulty to the saturated ketone, hexahydropyrethron, $C_{11}H_{20}O$, which is therefore monocyclic.²¹ (*N.B.* Staudinger and Ruzicka regarded the formula of pyrethrolone as being $C_{11}H_{16}O_2$, whereas later work, to be described below, has shown that it is $C_{11}H_{14}O_2$. Some of the hydrogenation products of pyrethrolone were therefore misnamed and the corrected names are used here.) Oxidation of hexahydropyrethron by permanganate yielded *n*-hexoic and lævulic acid. That the carbonyl group is in the ring was shown by Beckmann rearrangement of hexahydropyrethron oxime, by which a lactam (not an amide) was formed, which was converted by hydrochloric and then nitrous acid into a lactone, oxidised by permanganate to hexoic and lævulic acid. Hexahydropyrethron is therefore (XII),²¹ the lactam (XIII), and the lactone (XIV). This was confirmed by the Reformatski condensation of ethyl lævulate with ethyl α -bromoheptanoate to give (XV) in low yield, which was cyclised by the Dieckmann procedure and hydrolysed to 3-methyl-2-amylcyclopent-2-enone (XVI). This was reduced over nickel at 250° to 3-methyl-2-amylcyclopentanone (XII), identical with hexahydropyrethron.²² H. Staudinger and L. Ruzicka, regarding this as

¹⁹ *J. Org. Chem.*, 1945, **10**, 114. ²⁰ M. Elliott and S. H. Harper, unpublished work.

²¹ H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 236.

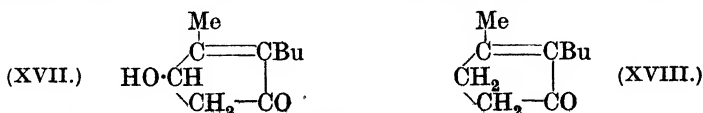
²² *Idem, ibid.*, p. 245.

the tetrahydro-stage, therefore formulated pyrethrolone as containing a *cyclopentanone* ring.



When H. L. Haller and F. B. LaForge repeated the isolation of pyrethrolone, they found that it and its derivatives analysed more satisfactorily for $\text{C}_{11}\text{H}_{14}\text{O}_2$ than for $\text{C}_{11}\text{H}_{16}\text{O}_2$.¹⁴ (Owing to ready autoxidation the combustion of these substances usually leads to low carbon values.) Pyrethrolone therefore contains an additional double bond, probably, because of its lack of reactivity, in the 2 : 3-position of the ring. This was confirmed by replacing the hydroxyl group of tetrahydropyrethrolone (XI) with chlorine by the action of thionyl chloride. The chloro-ketone was reduced with zinc to an optically inactive ketone, tetrahydropyrethron, the semicarbazone of which was identical with that of 3-methyl-2-amyl-*cyclopent*-2-enone (dihydrojasmon). Tetrahydropyrethron is therefore (XVI), and pyrethrolone is a hydroxy-3-methyl-2-pentadienyl*cyclopent*-2-enone. Although this degradative work was carried out before the recognition of the heterogeneity of pyrethrolone, it is reasonable to assume that traces of cinerolone were eliminated in the repeated purifications. Confirmation of the presence of the *cyclopent*-2-enone ring in pyrethrolone has been provided spectroscopically, for A. E. Gillam and T. F. West^{23, 24} have shown that pyrethrolone and its derivatives show the typical absorption (maximum at 2280 Å.) of an $\alpha\beta$ -unsaturated ketone in a five-atom ring.

Following the isolation of cinerolone, $\text{C}_{10}\text{H}_{14}\text{O}_2$, which therefore contains one carbon atom and one double bond less than pyrethrolone, this ketone was hydrogenated to dihydrocinerolone (XVII) and converted, through the chloro-ketone, into dihydrocinerone, identical with synthetic 3-methyl-2-butyl*cyclopent*-2-enone (XVIII),²⁵ and dihydrocinerone is therefore the



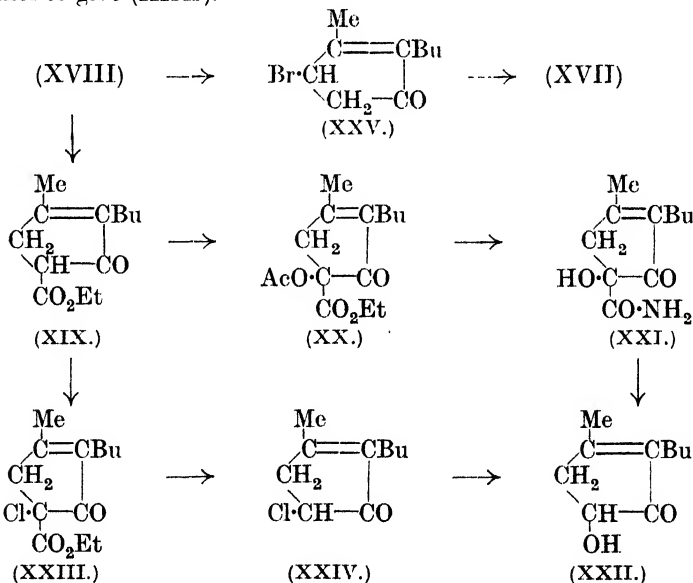
²³ J., 1942, 486, 671; 1944, 49.

²⁴ F. B. LaForge and F. Acree, *J. Org. Chem.*, 1942, 7, 416.

²⁵ F. B. LaForge and W. F. Barthel, *ibid.*, 1945, 10, 222.

lower homologue of tetrahydropyrethrone. The presence of the $\alpha\beta$ -unsaturated carbonyl group has similarly been confirmed spectroscopically.¹⁹

H. Staudinger and L. Ruzicka¹⁵ assigned the hydroxyl group of pyrethrolone to the 5-position on the basis of the reducing properties and apparent formation of a *p*-nitrophenylosazone. This conclusion remained unquestioned and on its discovery cinerolone was likewise assumed to have an α -keto-alcohol structure. However, in 1947 F. B. LaForge and S. B. Soloway²⁶ synthesised racemic 3-methyl-2-butylcyclopent-2-en-5-olone (XXII) and found that it was not identical with racemic dihydrocinerolone. A carbethoxy-group was introduced into (XVIII) by the action of diethyl carbonate and sodium hydride, and then an acetoxy-group by the action of lead tetra-acetate. Provided that the carbethoxy-group entered the methylene group adjacent to the carbonyl group, which is highly probable, then further substitution would lead to (XX), for lead tetra-acetate is without action on the unsubstituted ketone.²⁰ The carbethoxy-group was then eliminated by stepwise hydrolysis, cold ammonia giving the hydroxy-amide (XXI), from which hot aqueous sulphuric acid eliminated the amido-group. Alternatively, the sodio-derivative of (XIX) treated with toluene-*p*-sulphonyl chloride gave the chloro-ester (XXIII), from which the carbethoxy-group was eliminated by hydrochloric acid in acetic acid. The chloro-ketone (XXIV) was then hydrolysed by potassium formate in methanol to give (XXII).²⁷



Re-examination of dihydrocinerolone showed that it possessed only feeble reducing power and did not yield an osazone, whereas (XXII) behaved as a

²⁶ *J. Amer. Chem. Soc.*, 1947, **69**, 186.

²⁷ *Ibid.*, p. 2932.

typical α -keto-alcohol. F. B. LaForge and S. B. Soloway therefore suggested that cinerolone (and by implication pyrethrolone) is the 4-hydroxy-ketone. In support was cited the reactivity of the chloro-ketones obtained by the action of thionyl chloride on cinerolone, dihydrocinerolone, or tetrahydropyrethrolone, and the ready hydrogenolysis of the "pyrethrins,"²⁸ all suggestive of γ -substitution to an $\alpha\beta$ -unsaturated carbonyl group. Confirmation was obtained by the reaction of (XVIII) with *N*-bromosuccinimide to give a bromo-ketone, presumed to be (XXV) by analogy with the action of *N*-bromosuccinimide on $\alpha\beta$ -unsaturated ketones and esters. This was hydrolysed by aqueous calcium carbonate to racemic 3-methyl-2-butylcyclopent-2-en-4-olone (XVII), identical with racemic dihydrocinerolone.²⁹ In a similar manner, H. J. Dauben, jun., and E. Wenkert³⁰ established the 4-hydroxy-structure for the pyrethrolones by the action of *N*-bromosuccinimide upon (XVI). Hydrolysis of the resulting bromo-ketone with aqueous barium carbonate gave racemic 3-methyl-2-amylcyclopent-2-en-4-olone (XI), identical with racemic tetrahydropyrethrolone. L. Crombie, M. Elliott, S. H. Harper, and H. W. B. Reed³¹ have also prepared the 4-bromo-ketones from (XVIII) and (XVI), and treated these with silver acetate to give the 4-acetoxy-ketones, which were hydrolysed to (XVII) and (XI), respectively. Although the 4-position is the most probable point of substitution, there are three other positions at which *N*-bromosuccinimide might react. These, however, are all excluded, the 5-position by the previous syntheses by F. B. LaForge and S. B. Soloway,^{26, 27} and by the fact that tetrahydropyrethrolone is not oxidised by lead tetra-acetate^{20, 31a} or by periodic acid,³⁰ whilst substitution in the 3-methyl group is excluded by the terminal methyl contents of dihydrocinerolone and of tetrahydropyrethrolone,^{8, 19} and substitution in the 1'-position of the side-chain is excluded because oxidation of tetrahydropyrethrolone gives *n*-hexoic acid.¹⁵

F. B. LaForge and W. F. Barthel¹⁹ have shown that the isomeric pyrethrolones are reduced to the same tetrahydropyrethrolone. Kuhn-Roth oxidation (as modified by W. F. Barthel and F. B. LaForge³²) gave similar terminal methyl values which were taken to indicate the presence of only one terminal methyl group, so that there is a terminal methylene group to the side-chain.

On the basis of earlier work LaForge and Barthel adopted a conjugated position for the two double bonds. This has been confirmed by West⁸ who showed that the isomeric pyrethrolone semicarbazones show similar absorption maxima at 2655 μ . corresponding to the C:C:C:N system and another band at 2310 μ . due to a conjugated diene system in the side-chain separate from the C:C:C:N system. The pyrethrolones are therefore

²⁸ H. L. Haller and F. B. LaForge, *J. Org. Chem.*, 1937, **2**, 49; F. B. LaForge and F. Acree, *Soap*, 1941, **17**, No. 1, 95; F. B. LaForge and B. B. Bendigo, *ibid.*, 1943, **19**, No. 4, 100.

²⁹ S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, 1947, **69**, 979.

³⁰ *Ibid.*, p. 2074.

³¹ *Nature*, 1948, **162**, 222.

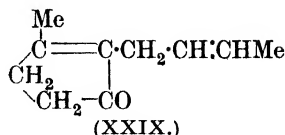
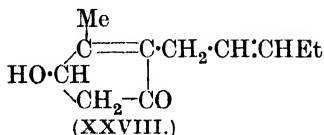
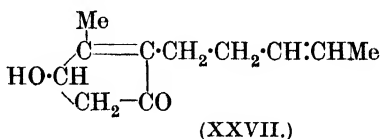
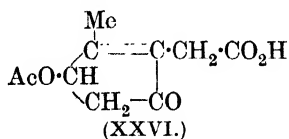
^{31a} E. Baer and T. F. West, *J.*, 1949, 93.

³² *Ind. Eng. Chem. Anal.*, 1944, **16**, 434.

3-methyl-2-penta-2':4'-dienylcyclopent-2-en-4-olones (VII), and must be geometrical isomers about the 2'-double bond. By analogy with *cis*- and *trans*-piperylene the *trans*-pyrethrolone should participate in Diels-Alder-type additions with dienophiles. Examination of the isomeric pyrethrolones for this has not been described, although F. B. LaForge and H. L. Haller³³ found that "pyrethrolone" did not react with α -naphthaquinone, whilst T. F. West^{33a} showed that "pyrethrolone" methyl ether similarly did not react with dienophiles. If it is assumed that in these experiments the major component of "pyrethrolone" predominated (that giving the higher-melting semicarbazone), then this isomer should have the *cis*-configuration.

The ozonolysis of these isomeric pyrethrolones has not been described. The production of formaldehyde on ozonolysis of earlier preparations of "pyrethrolone" has been recorded.³³ The formaldehyde was then generally regarded as arising from impurity, while the acetaldehyde also produced was believed to be derived from the pyrethrolone; this led to structures for pyrethrolone containing the cumulated penta-2':3'-dienyl^{15, 24, 33, 34, 35} or the conjugated penta-1':3'-dienyl^{16, 23, 36} side-chains, which have now been discarded. H. Staudinger and L. Ruzicka¹⁵ isolated malonic acid and an acetoxy-acid, $C_{10}H_{12}O_5$, from the ozonolysis of pyrethrolone acetate, which is evidently (XXVI), and support the 2'-position for the other double bond.

The terminal methyl values of the pyrethrolones are 10–20% greater than that calculated for one methyl group, whereas the reverse is more usual. F. B. LaForge and W. F. Barthel¹⁹ therefore suggest that dihydropyrethrolones may be present, which would, of course, add to the number of possible "pyrethrins." (XXVII) or (XXVIII) are possible structures.



F. B. LaForge and W. F. Barthel¹⁹ similarly assigned a but-2'-enyl structure to the side-chain of cinerolone, for Kuhn-Roth oxidation indicated two terminal methyl groups. This is supported spectroscopically, for

³³ F. B. LaForge and H. L. Haller, *J. Org. Chem.*, 1938, **2**, 546.

^{33a} *J.*, 1944, 239.

²⁴ F. B. LaForge and H. L. Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1061.

³⁵ F. Acree and F. B. LaForge, *J. Org. Chem.*, 1939, **4**, 569; 1940, **5**, 48, 430; F. B. LaForge and F. Acree, *J. Amer. Chem. Soc.*, 1940, **62**, 1621; *J. Org. Chem.*, 1941, **6**, 208.

³⁶ L. Ruzicka and M. Pfeiffer, *Helv. Chim. Acta*, 1933, **16**, 1208.

cinerolone semicarbazone shows only the absorption (maximum at 2655 Å.) of the C:C:C:N system.⁸ Cinerolone is therefore 3-methyl-2-but-2'-enylcyclopent-2-en-4-olone (VIII). S. H. Harper³⁷ has ozonised a specimen of *dextro*cinerolone, prepared by T. F. West, and obtained acetaldehyde together with a small proportion of formaldehyde. The origin of the formaldehyde is not clear; it is unlikely that it is due to pyrethrolone, but it may indicate the presence of the but-3'-enyl isomer of cinerolone. Nevertheless it is confirmed that the major component has the but-2'-enyl structure.

In contrast to pyrethrolone the hydroxyl group of cinerolone can be replaced by hydrogen, by way of the chloro-ketone, to give cinerone (XXIX).¹⁹ An attempt to confirm this structure for cinerone was made by S. H. Harper.³⁸ Methyl dec-8-ene-2:5-dione-4-carboxylate was cyclised by aqueous alkali to 3-methyl-2-but-2'-enylcyclopent-2-enone (XXIX), which resembled cinerone closely, but both the semicarbazones and the *p*-nitrophenylhydrazones gave depressions of melting point. The synthetic ketone has the *trans*-configuration having been derived ultimately from *trans*-crotonaldehyde. L. Crombie and S. H. Harper³⁹ have confirmed this configuration by another synthesis starting from furan.

The synthetic semicarbazone has the higher melting point, and is colourless and stable, whereas the semicarbazones of cinerone and cinerolone are yellow and deteriorate on keeping. It is therefore concluded that cinerone, and hence cinerolone, has the *cis*-configuration. This is supported by the work of F. B. LaForge, N. Green, and W. A. Gersdorff,⁴⁰ who have also synthesised (XXIX), starting from crotyl chloride, and obtained a *p*-nitrophenylhydrazone which raised the melting point of the *p*-nitrophenylhydrazone of cinerone. The crotyl chloride used had presumably been made by chlorination of the mixed *cis*- and *trans*-but-2-enes and would therefore give a *cis-trans* mixture of (XXIX) in which the *cis*-form might predominate. However, as both *cis*- and *trans*-pyrethrolone occur in Nature, *trans*-cinerolone may also be present in "pyrethrolone."

Chrysanthemum-monocarboxylic acid together with its methyl ester was obtained by H. Staudinger and L. Ruzicka⁴¹ from the sodium methoxide fission of the mixed semicarbazones of the "pyrethrins." It is now more conveniently obtained together with the dicarboxylic acid by the direct hydrolysis of pyrethrum extract. It is readily isolated by reason of its steam volatility and solubility in light petroleum. Originally obtained as a liquid, it is now recognised as being a low-melting crystalline solid, having been first crystallised by F. Wilcox.⁴² Hydrogenation gave the dihydro-acid,⁴¹ also obtained on the hydrogenolysis of "pyrethrin I,"²⁸ which reveals that it is monocyclic. The structure of chrysanthemum-monocarboxylic acid as *dextro-trans*-2:2-dimethyl-3-isobutenylcyclopropane-1-carboxylic acid (V) followed from ozonisation which yielded *laevo-trans*-caronic acid (XXX) and acetone.

³⁷ Unpublished work.

³⁸ Unpublished work.

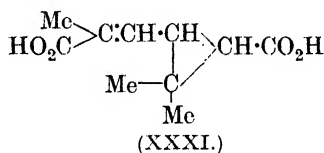
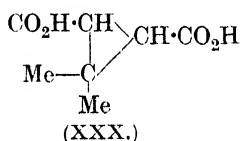
⁴¹ *Helv. Chim. Acta*, 1924, **7**, 201.

³⁸ *J.*, 1946, 892.

⁴⁰ *J. Amer. Chem. Soc.*, 1948, **70**, 3707.

⁴² *Contrib. Boyce Thompson Inst.*, 1936, **8**, 175.

H. Staudinger, O. Muntwyler, L. Ruzicka, and S. Seibt⁴³ attempted to confirm this structure by synthesis. Addition of ethyl diazoacetate to 2 : 5-dimethylhexa-2 : 4-diene, followed by hydrolysis, gave a low yield of crystalline racemic *cis*-chrysanthemum-monocarboxylic acid (using chrysanthemum-mono- and -di-carboxylic acids as names for the structures (V) and (XXXI) and not limiting them to the particular stereoisomers present in pyrethrum flowers). The racemic *trans*-acid was not isolated, but its presence in the oily mother-liquor was demonstrated by the formation of racemic *trans*-caronic acid on ozonisation. No comparison with the natural acid was therefore possible. I. G. M. Campbell and S. H. Harper⁴⁴ were able to develop this route to give both the racemic *cis*- and crystalline *trans*-acids in good yield. Resolution of the *trans*-acid was effected through the quinine salt to give optically pure *laevo-trans*-acid, which proved to be the enantiomorph of the natural acid. The *dextro-trans*-configuration of the natural acid is therefore confirmed.



The dextrorotatory non-steam-volatile chrysanthemumdicarboxylic acid was obtained by H. Staudinger and L. Ruzicka,⁴¹ together with the mono- and di-methyl esters, from the sodium methoxide fission of the mixed semicarbazones of the "pyrethrins," and arises from the "pyrethrin II." The dicarboxylic acid itself had earlier been isolated by J. Fujitani.⁴ The dicarboxylic acid resisted hydrogenation, but its structure as (XXXI) followed from ozonisation which yielded *laevo-trans*-caronic acid (XXX) and pyruvic acid, whilst that of the monomethyl ester as (VI) followed from the similar isolation of (XXX) and methyl pyruvate. It thus has the same *dextro-trans*-configuration as the monocarboxylic acid (with reference to the ring, for the configuration of the side-chain is unknown). That "pyrethrin II" is actually derived from this monomethyl ester (although it was obtained under conditions promoting transesterification and might therefore have been an artefact) was suggested by H. Staudinger and L. Ruzicka, who showed that the "pyrethrins" contained the methoxyl group, identified by hydrolysis and then conversion into tetramethyl-ammonium iodide. Later work has confirmed that "pyrethrin II" contains methoxyl,⁴⁵ whilst the 100% "pyrethrin II" prepared by A. E. Gillam and T. F. West¹⁸ analysed correctly. H. L. Haller and F. B. LaForge⁴⁶ subjected "pyrethrin II" concentrates to hydrogenolysis in non-methanolic media, and obtained what was first described as the monomethyl ester of chrysanthemumdicarboxylic acid, but later as the mono-

⁴³ *Helv. Chim. Acta*, 1924, 7, 390.

⁴⁴ *J.*, 1945, 283.

⁴⁵ H. L. Haller and F. B. LaForge, *Ind. Eng. Chem. Anal.*, 1935, 7, 343.

⁴⁶ *J. Org. Chem.*, 1937, 2, 49.

methyl ester of dihydrochrysanthemumdicarboxylic acid.⁴⁷ Although this acid was characterised only by a determination of the equivalent, this would exclude any other formulation.

"Pyrethrin I" and "pyrethrin II," of varying heterogeneity, have been resynthesised from "pyrethrolone" and the acid chlorides of the natural monocarboxylic acid and the monomethyl ester of the dicarboxylic acid with pyridine or quinoline in benzene.^{48, 49} These resynthesised pyrethrins, however, differed from their natural counterparts in failing to give semicarbazones. However, H. L. Haller and F. B. LaForge⁴⁹ successfully resynthesised "tetrahydropyrethrin I" and "tetrahydropyrethrin II" which gave crystalline semicarbazones. More recently F. B. LaForge and W. F. Barthel⁴⁷ have resynthesised racemic (with respect to the alcohol) and *laevopyrethrin* I, pyrethrin II, cinerin I, and cinerin II, of which only the *laevopyrethrin* I and *laevocinerin* I gave semicarbazones. The explanation of the earlier failures may therefore have been due to racemisation of the "pyrethrolone."

The total synthesis of the pyrethrins depends on successful syntheses of pyrethrolone and cinerolone which have not yet been accomplished. H. Staudinger and L. Ruzicka⁵⁰ made a very intensive effort to synthesise pyrethrolone, but as they were working to a formula now known to be incorrect they were doomed to failure. L. Crombie, M. Elliott, S. H. Harper, and H. W. B. Reed³¹ treated the 4-bromo-ketones, derived from synthetic (XVIII) and (XVI), with the silver salts of *cis*- and *trans*-chrysanthemum-monocarboxylic acids⁴⁴ and obtained fully racemic *cis*- and *trans*-dihydro-cinerin I and *cis*- and *trans*-tetrahydropyrethrin I. The extension of this route to a synthesis of a cinerin I, by the action of *N*-bromosuccinimide on *trans*-cinerone, has not yet proved feasible, presumably owing to competing substitution in the side-chain.^{20, 40} F. B. LaForge, N. Green, and W. A. Gersdorff⁴⁰ have prepared analogues of cinerin I with the hydroxyl group in the 5-position. A 5-hydroxyl group was introduced into synthetic cinerone and 3-methyl-2-but-3'-enylcyclopent-2-enone (earlier prepared by S. H. Harper³⁸) by the method used earlier by F. B. LaForge and S. B. Soloway.²⁶ The resulting structural isomers of cinerolone were then esterified with natural chrysanthemum-monocarboxylic acid. Both the resynthesised "pyrethrins" and the synthetic analogues have been tested for insecticidal properties with results that are now throwing some light on the relationship of toxicity to chemical structure. Exigencies of space prevent any account of this aspect of pyrethrum chemistry being given here, and the reader should refer to the original papers cited above and to the following papers.⁵¹

⁴⁷ F. B. LaForge and W. F. Barthel, *J. Org. Chem.*, 1947, **12**, 199.

⁴⁸ H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 488; F. Tattersfield, R. P. Hobson, and C. T. Gimingham, *J. Agr. Sci.*, 1929, **19**, 266.

⁴⁹ H. L. Haller and F. B. LaForge, *J. Amer. Chem. Soc.*, 1937, **59**, 1678.

⁵⁰ *Helv. Chim. Acta*, 1924, **7**, 377, 406, 442.

⁵¹ H. L. Haller and W. N. Sullivan, *J. Econ. Entomol.*, 1938, **31**, 276; R. G. Green, W. Pohl, F. H. Tresadern, and T. F. West, *J. Soc. Chem. Ind.*, 1942, **61**, 173r; W. A. Gersdorff, *J. Econ. Entomol.*, 1947, **40**, 878.

Likewise no account has been given of aspects that do not have a direct bearing on the elucidation of the structure of the pyrethrins.

Diterpenes.

The resin acids and resinols were last reviewed here as a group in 1936,¹ although further work on abietic acid was reported in 1941.² Since the former report there has been much interesting work directed towards the elucidation of the structures of other resin acids and of their stereochemical interrelations. The former has been facilitated by advances made in the methods of separation of the primary resin acids, *e.g.*, the use of maleic anhydride adducts and of the fractional crystallisation of salts with aliphatic amines. In fact, G. C. Harris³ has made a total analysis of the acid fraction of the oleoresin of American *Pinus palustris*, using these techniques supplemented by ultra-violet-absorption-spectra measurements. This has disclosed that abietic acid (the laevorotatory form), hitherto only obtained as a transformation product, by the action of heat or mineral acids, of the primary resin acids, is itself a primary constituent. Using these methods proabietic acid¹ has been shown to be a mixture of other resin acids.⁴ R. Lombard⁵ has described a dextrorotatory sapinic acid (earlier called alepic acid), but its physical constants are so close to those of a dihydroabietic acid prepared by G. Brus and E. Levy⁶ as to suggest that it is in fact the latter. Further, E. E. Fleck and S. Palkin⁷ have shown that dihydroabietic acid is a primary constituent of pine oleoresin.

In the earlier reports^{1,2} the evidence establishing the structure of abietic acid as (I) was summarised.* (Several methods of lettering and numbering this ring system are in use. That employed here is used by the Swiss workers and by H. H. Zeiss.⁸) Abietic acid of higher melting point and specific rotation has been prepared through the bornylamine⁹ or diamylamine¹⁰ salt, which suggests that earlier preparations may have been impure. This is supported by the isolation of a small percentage of acetone on ozonolysis.¹¹ Without doubt the impurity is neoabietic acid (II), which has been isolated by G. C. Harris and T. F. Sanderson¹⁰ from the

¹ *Ann. Reports*, 1936, **33**, 267.

² *Ibid.*, 1941, **38**, 187.

³ *J. Amer. Chem. Soc.*, 1948, **70**, 3671.

⁴ G. C. Harris and J. Sparks, *ibid.*, 1948, **70**, 367.

⁵ *Compt. rend.*, 1944, **219**, 587; *Bull. Soc. chim.*, 1944, **11**, 201; 1945, **12**, 395; see, however, *ibid.*, 1948, **15**, 1186, where Lombard suggests that sapinic acid is the 6:7-9:14 isomer of abietic acid.

⁶ *Ibid.*, 1939, **6**, 78.

⁷ *J. Amer. Chem. Soc.*, 1939, **61**, 1230.

⁸ *Chem. Reviews*, 1948, **42**, 163.

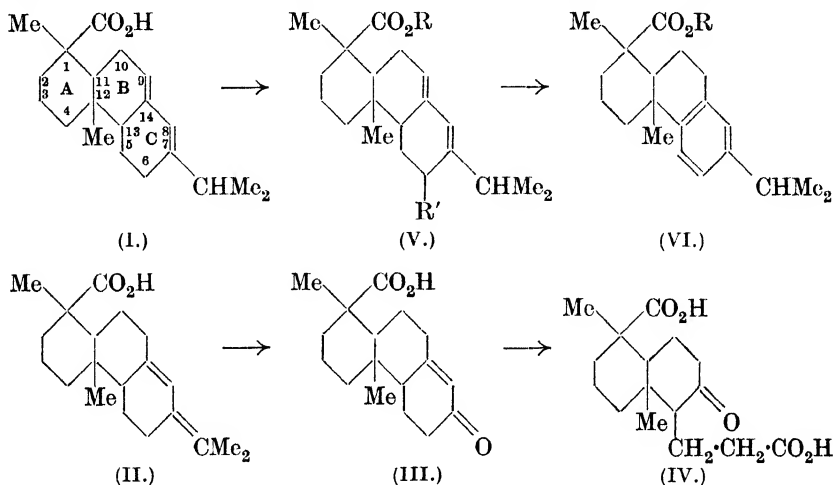
⁹ I. I. Bardishev, *J. Gen. Chem. Russia*, 1941, **11**, 996; cf. G. A. Garkuscha, *ibid.*, 1938, **8**, 1042; R. Lombard and J. M. Frey, *Bull. Soc. chim.*, 1948, **15**, 1194.

¹⁰ G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 334.

¹¹ H. Raudnitz, N. Lederer, and E. Kahn, *Ber.*, 1938, **71**, 1273.

* The final proof of the structure of abietic acid by its conversion into 8-azaretene (L. Ruzicka, L. Sternbach, and O. Jeger, *Helv. Chim. Acta*, 1941, **24**, 504) was subsequently completed by synthesis of the latter (L. Ruzicka, L. Sternbach, and C. Kauter, *ibid.*, 1942, **25**, 1036).

oleoresin of *P. palustris* as the diethylamine salt. It is isomerised by mineral acids to abietic acid, and gives retene on dehydrogenation. Its structure as (II) follows from its absorption maximum at 2500 Å., which is in close agreement with that predicted for a conjugated diene in this environment (2520 Å.).¹² Limited ozonisation yielded acetone and an $\alpha\beta$ -unsaturated ketone (III) (λ_{\max} , 2420 Å., predicted 2390 Å.), whilst complete ozonisation and dehydrogenation of the keto-acid (IV) gave 1-methyl-5-*n*-propylnaphthalene, clearly establishing this structure for *neoabietic acid*.¹³



W. Sandermann and R. Höhn¹⁴ obtained a dextrorotatory abietic acid, *isoabietic acid*, by thermal degradation of the maleic-anhydride adduct of sapietic acid and also from abietic acid dihydrobromide by dehydrobromination. T. Hasselstrom and J. D. McPherson¹⁵ had earlier prepared a similar acid by the latter method. The Reporter suggests that *isoabietic acid* is probably identical with rubeabietic acid¹⁶ and with α - and γ -sapinic acids.¹⁷ *isoAbietic acid* gave abietic acid dihydrobromide with hydrogen bromide, and the adduct of sapietic acid with maleic anhydride. The absorption maximum indicates the presence of two conjugated double bonds, which do not lie in one ring. Mild oxidation with permanganate followed by chromic acid gave acetone, whilst vigorous permanganate oxidation gave *isobutyric acid*. The Reporter suggests that these results are best explained if *isoabietic acid* is a mixture of abietic and *neoabietic*

¹² R. B. Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72.

¹³ G. C. Harris and T. F. Sanderson, *Ber.*, 1948, **70**, 339.

¹⁴ *Ber.*, 1943, **76**, 1257, 1261.

¹⁵ *J. Amer. Chem. Soc.*, 1939, **61**, 2247.

¹⁶ M. Kono and R. Maruyama, *J. Agr. Chem. Soc. Japan*, 1937, **13**, 177; 1938, **14**, 318.

¹⁷ V. N. Krestinski, A. Novak, and N. F. Komschilov, *J. Appl. Chem. Russia*, 1939, **12**, 1514; V. N. Krestinski, N. F. Komschilov, and E. V. Kazeeva, *ibid.* p. 1840; V. N. Krestinski, E. V. Kazeeva, and N. F. Komschilov, *ibid.*, 1941, **14**, 229.

acids. Furthermore, its specific rotation ($[\alpha]_D +21^\circ$) is consistent with its being a 1 : 1 molecular complex (abietic acid, $[\alpha]_D -105^\circ$ to -115° ; *neo*-abietic acid, $[\alpha]_D +159^\circ$).

Dehydroabietic acid (VI; $R = H$), first prepared by L. F. Fieser and W. P. Campbell¹⁸ by oxidising abietic acid with selenium dioxide to 6-hydroxyabietic acid (V; $R = H$, $R' = OH$) and dehydrating this in acetic acid, has now been prepared by the action of *N*-bromosuccinimide on methyl abietate to give, presumably, (V; $R = Me$, $R' = Br$) which is dehydrobrominated by sodium acetate in acetic acid.¹⁹ Dehydroabietic acid, together with dihydro- and tetrahydro-abietic acids, has also been obtained by the thermal disproportionation or dehydrogenation of abietic acid,²⁰ in the presence of palladium-charcoal,²¹ iodine,²² or sulphur.²³ Dehydroabietic acid has been identified spectroscopically in the primary resin acids that do not react with maleic anhydride,³ which, with the dihydro-abietic acid also present, suggests that some disproportionation of abietic acid occurs in Nature. The benzenoid character of ring C of dehydroabietic acid has been demonstrated by typical aromatic substitution in the 6- and 8-positions.^{18, 24} A dehydroabietic acid was synthesised by R. D. Haworth and R. L. Barker,²⁵ but comparison with the natural acid awaits resolution of the synthetic acid.

Lævorotatory sapietic acid was formerly called *l*-pimaric acid in the erroneous belief that it is the enantiomorph of pimaric acid. Confusion is still caused, and it would appear highly desirable to discontinue the use of the terms *lævopimaric* or *levopimaric* for other than the true enantiomorph of dextrorotatory pimaric acid.¹ Sapietic acid, the major constituent of the primary resin acids of the oleoresin of *P. palustris* and the main precursor of abietic acid, is now readily isolated as the *tert*.-butanolamine salt.¹⁰ There is now little doubt that sapietic acid has the structure (VII) formerly assigned to abietic acid.¹ Maleic anhydride reacts at room temperature to give an adduct, only obtained from abietic acid at temperatures above 80° .²⁶ Ozonisation gives isobutyric acid which places one of the double bonds at 6 : 7 or 7 : 8.²⁷ The ease of addition of dienophiles and the absorption

¹⁸ *J. Amer. Chem. Soc.*, 1938, **60**, 159.

¹⁹ O. Jeger, O. Dürst, and G. Büchi, *Helv. Chim. Acta*, 1947, **30**, 1853.

²⁰ E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.*, 1938, **60**, 921.

²¹ *Idem*, *Science*, 1937, **85**, 126; *J. Amer. Chem. Soc.*, 1937, **59**, 1593; E. R. Littmann, *ibid.*, 1938, **60**, 1419; L. Ruzicka, R. G. R. Bacon, L. Sternbach, and H. Waldmann, *Helv. Chim. Acta*, 1938, **21**, 591.

²² T. Hasselstrom, E. A. Brennan, and S. Hopkins, junr., *J. Amer. Chem. Soc.*, 1941, **63**, 1759.

²³ R. Lombard, *Compt. rend.*, 1941, **213**, 793; *Bull. Soc. chim.*, 1942, **9**, 833.

²⁴ W. P. Campbell and M. Morgana, *J. Amer. Chem. Soc.*, 1941, **63**, 1838; L. F. Fieser and W. P. Campbell, *ibid.*, 1938, **60**, 2631; 1939, **61**, 2528; T. Hasselstrom, E. A. Brennan, and J. D. McPherson, *ibid.*, 1938, **60**, 1267.

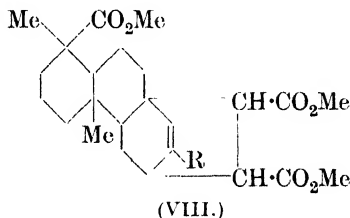
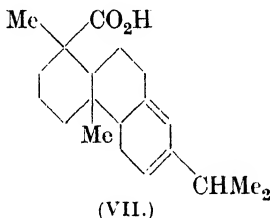
²⁵ *J.*, 1939, 1299.

²⁶ L. Ruzicka and R. G. R. Bacon, *Chem. and Ind.*, 1936, **55**, 546; *Helv. Chim. Acta*, 1937, **20**, 1542; H. Wienhaus and W. Sandermann, *Ber.*, 1936, **69**, 2202.

²⁷ L. Ruzicka, R. G. R. Bacon, R. Lukes, and J. D. Rose, *Helv. Chim. Acta*, 1938, **21**, 583.

maximum at 2725 μ .²⁸ confirm that the two double bonds are conjugated and both in ring C. This permits four alternatives, 13 : 5-6 : 7, 5 : 6-7 : 8, 7 : 8-14 : 13, and 6 : 7-8 : 14, of which the last is preferred.^{29, 30, 31}

In an attempt to distinguish between these alternatives L. Ruzicka and S. Kaufmann²⁹ obtained rather curious results. Ozonolysis of the trimethyl ester of the maleic anhydride adduct of sapietic acid gives a singly unsaturated keto-triester and a doubly unsaturated triester, both crystalline. The former gives the haloform reaction indicating the presence of $\cdot\text{COMe}$, whilst its absorption maximum at 2390 μ . is consistent with its being a doubly substituted $\alpha\beta$ -unsaturated ketone. Ruzicka and Kaufmann formulated this as (VIII; $\text{R} = \text{COMe}$). The doubly unsaturated triester shows an absorption maximum at 2400 μ ., and is hydrogenated back to the original triester. Ruzicka and Kaufmann formulated this as (VIII; $\text{R} = \text{CMe}\cdot\text{CH}_2$), although this type of diene usually absorbs at 2320 μ . Presumably ozone hydroxylates the tertiary carbon atom of the *isopropenyl* group; this is followed by dehydration to the *isopropenyl* group (the doubly unsaturated triester), and further ozonolysis gives an acetyl group (the singly unsaturated keto-triester). These results are regarded as excluding the 13 : 5-6 : 7-, 5 : 6-7 : 8-, and 7 : 8-14 : 13-positions for the double bonds of sapietic acid.



Dihydroabietic acids of a wide range of melting points and specific rotations have been reported to result from the hydrogenation of abietic acid, some of which are presumably mixtures.³² Nevertheless, several of these acids yield the same lactone with cold mineral acid. T. Hasselstrom and J. D. McPherson³³ suggested that it is a γ -lactone formed by lactonisation at position 10 of a 9 : 10-double bond. Nevertheless, it is likely that the residual double bond would be at positions 7 : 8, 8 : 14, or 9 : 14,

²⁸ K. Kraft, *Annalen*, 1935, **520**, 133.

²⁹ L. Ruzicka and S. Kaufmann, *Helv. Chim. Acta*, 1940, **23**, 1346; L. Ruzicka, W. A. Lalande, junr., and S. Kaufmann, *ibid.*, p. 1357.

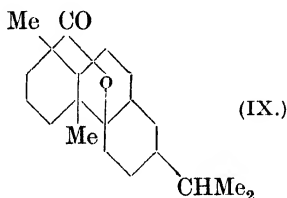
³⁰ S. S. Malevskaja, *J. Appl. Chem. Russia*, 1940, **13**, 1085; B. A. Arbusov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **30**, 723; *J. Gen. Chem. Russia*, 1942, **12**, 343.

³¹ W. Sandermann, *Ber.*, 1941, **74**, 154; W. Sandermann and R. Höhn, *ibid.*, 1943, **76**, 1257.

³² E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.*, 1938, **60**, 2621; T. Hasselstrom, E. A. Brennan, and J. D. McPherson, *ibid.*, 1938, **60**, 1267; T. Hasselstrom and J. D. McPherson, *ibid.*, 1939, **61**, 1228; L. Ruzicka, R. G. R. Bacon, L. Sternbach, and H. Waldmann, *Helv. Chim. Acta*, 1938, **21**, 565; L. Ruzicka and S. Kaufmann, *ibid.*, 1941, **24**, 1389; R. Lombard, *Bull. Soc. chim.*, 1944, **11**, 526.

³³ *J. Amer. Chem. Soc.*, 1938, **60**, 2340.

and, provided that the configuration of rings A and B permitted, the last could δ -lactonise at position 9. E. E. Fleck and S. Palkin,³⁴ however, suggested that in the presence of mineral acid the 8 : 14- or 9 : 14-double bonds might shift to the 13 : 14-position permitting δ -lactone formation on position 13 (IX), but again this would depend on the configuration of rings A and B. Opening the lactone ring with alkali gave a hydroxytetrahydroabietic acid which failed to give a ketone on oxidation, indicating a tertiary carbon atom for the point of lactonisation, although the ease of re-lactonisation makes this negative evidence equivocal. R. F. B. Cox³⁵ treated the lactone with methylmagnesium iodide and obtained a *lævo*- and a *dextro*-rotatory dihydroabietic acid, easily reconverted into the lactone by mineral acid. Nitrosyl chloride converted the former into a blue tertiary nitroso-lactone, whilst the latter yielded an oximinolactone. This was regarded as confirming lactonisation at position 13, the *lævo*rotatory acid containing a 13 : 14-double bond, and the *dextro*rotatory acid a 5 : 13-double bond. The structure of this lactone has an important bearing on the configurations at C₁, C₁₁, and C₁₂ in abietic acid, and is referred to below in this connection.



At the time of the last report on *dextro*rotatory pimaric acid³⁶ its structure had been limited to the alternatives (X) and (XI), rings A and B being identical with those in abietic acid. Ruzicka preferred (X) as being in accord with the ready dehydrogenation to pimanthrene (1 : 7-dimethylphenanthrene), whereas (XI) might be expected to yield both pimanthrene and 1-methyl-7-ethylphenanthrene. The absence of the latter product cannot now be regarded as evidence against (XI), for it is recognised that on dehydrogenation of a *gem*-dialkyl group, *e.g.*, *gem*-methylethyl,³⁷ the larger of the two groups is extruded exclusively.

L. Ruzicka and L. Sternbach³⁸ hydrogenated the exocyclic double bond of methyl pimarate to give methyl dihydropimarate (XII or XIII; R = Me), the dibromide or the oxide of which, on treatment with methylmagnesium iodide, followed by selenium dehydrogenation, gave 1 : 7 : 8-trimethylphenanthrene. Although this clearly demonstrates that the second double bond is at 7 : 8 or 8 : 14, it does not suffice to distinguish between (XII) and (XIII). T. Hasselstrom and B. L. Hampton³⁹ found that dihydropimaric acid lactonised in cold mineral acid as does dihydroabietic acid, whilst

³⁴ *J. Amer. Chem. Soc.*, 1939, **61**, 3197.

³⁵ *Ibid.*, 1944, **66**, 865.

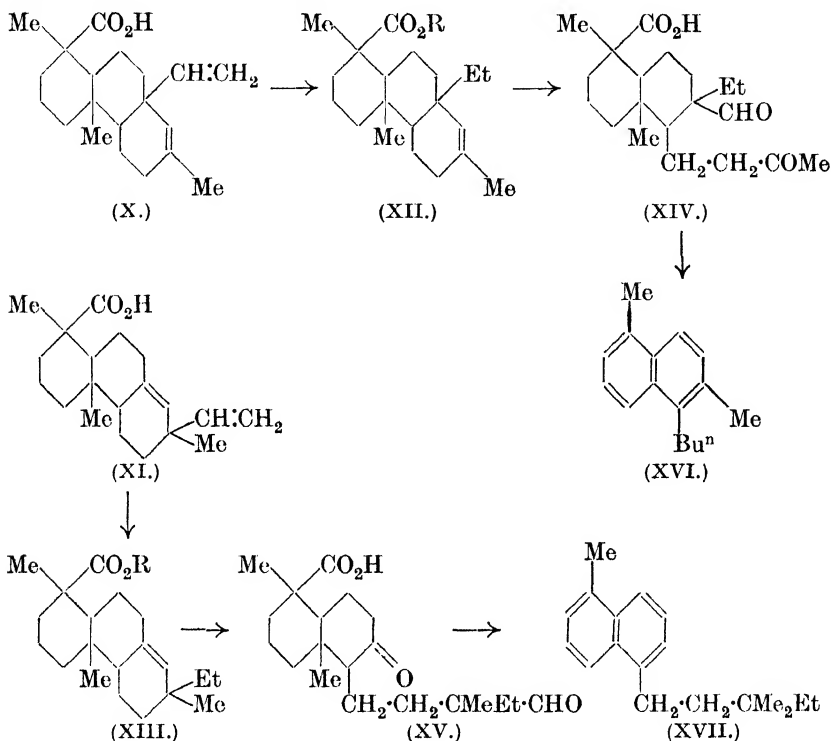
³⁶ *Ann. Reports*, 1932, **29**, 159.

³⁷ R. L. Barker and G. R. Clemo, *J.*, 1940, 1277.

³⁸ *Helv. Chim. Acta*, 1940, **23**, 124.

³⁹ *J. Amer. Chem. Soc.*, 1939, **61**, 967.

E. E. Fleck and S. Palkin⁴⁰ working at -30° obtained a hydroxy-lactone in which the hydroxyl group is tertiary. These observations exclude (XII) if, as Fleck and Palkin suggest, the 8 : 14-double bond of (XIII) shifts under the influence of acid to position 13 : 14, permitting δ -lactone formation on C₁₃. This cannot occur with (XII), and thus indicates (XI) instead of (X) as the structure of pimonic acid.



G. C. Harris and T. F. Sanderson⁴¹ have now provided a complete proof of the correctness of (XI). Dihydropimonic acid (XII or XIII; R = H) on ozonolysis gave a keto-aldehyde (XIV or XV) which failed to give the iodoform test. Although this is negative evidence it excludes (XIV) and favours (XI) as the structure of pimonic acid. However, Kishner-Wolff reduction of this keto-aldehyde and dehydrogenation yielded a 1 : 5-dialkylnaphthalene carefully characterised as a C₁₈ hydrocarbon. This can only be (XVII), and hence established (XI) as the structure of pimonic acid.

Recently G. C. Harris and T. F. Sanderson⁴² have isolated an isomer of pimonic acid, "isodextropimonic acid" by fractional crystallisation of the *tert.*-butanolamine salts of the pimonic acid fraction. (*N.B.* If sapietic

⁴⁰ *J. Amer. Chem. Soc.*, 1940, **62**, 2044. ⁴¹ *Ibid.*, 1948, **70**, 2081. ⁴² *Ibid.*, p. 2079.

acid was generally used the terms levopimaric and dextropimaric would not be required: their introduction seems retrogressive.) Like pimaric acid it yields formaldehyde on ozonisation and pimanthrene on dehydrogenation. It shows no absorption maximum in the ultra-violet indicating the absence of conjugation. Harris and Sanderson⁴¹ have related this acid to pimaric acid by isolating the same C_{18} hydrocarbon (XVII) as from pimaric acid. They therefore concluded that "isodextropimaric acid" is the diastereoisomer (about C_7) of pimaric acid. This was supported by eliminating the asymmetry of C_7 by ozonisation of the two acids to give the same keto-tricarboxylic acid (XVIII). Partial dehydrogenation of the two acids and chromatography on silica gel yielded the same trisubstituted naphthalene hydrocarbon (XIX), further dehydrogenated to pimanthrene. It is not clear to the Reporter how the double bond of the vinyl group migrates to the ring without extrusion of one of the alkyl groups. The Reporter would expect the diastereomer of dextrorotatory pimaric acid to be optically active, whereas "isodextropimaric acid" and all of its derivatives are optically inactive. These results appear to be equally well explained if "isodextropimaric" is in fact racemic pimaric acid.

Quite recently G. C. Harris and T. F. Sanderson⁴³ have shown that the diterpene ketone, "cryptopinone," originally isolated from *P. sylvestris*,⁴⁴ is also present in the neutral fraction of *P. palustris* and *P. caribaea* resin. Moreover, it is an aldehyde, and on chromic acid oxidation gives "isodextropimaric acid." Harris and Sanderson therefore rename it "isodextropimarinal" and formulate it as (XX). C. W. Brandt and L. G. Neubauer⁴⁵ isolated miropinic and isomiropinic acids from *Podocarpus ferrugineus* resin, isomeric with pimaric acid and giving pimanthrene on dehydrogenation. Miropinic acid is probably identical with cryptopimaric acid from *Cryptomeria japonica*,⁴⁶ and with acids isolated from *Dacrydium biforme*⁴⁷ and *D. Kirkii*,⁴⁸ but in no case has the detailed structure been elucidated.

Although the dextrorotatory resin acid, podocarpic acid, $C_{17}H_{22}O_3$, is not a true diterpene, its structure has a direct bearing on that of abietic acid, and hence justifies brief consideration here. I. R. Sherwood and W. F. Short⁴⁹ showed that it was phenolic and that sulphur dehydrogenation yielded 6-hydroxy-1-methylphenanthrene. The carboxyl group shows much greater resistance to esterification and hydrolysis than does the carboxyl group of dehydroabietic acid (VI; $R = H$). Structure (XXI; $R = H$) was therefore tentatively suggested. Shortly afterwards L. F. Fieser and W. P. Campbell⁵¹ suggested that it might be (XXII; $R = H$) analogous

⁴³ *J. Amer. Chem. Soc.*, 1948, **70**, 3870.

⁴⁴ N. A. Sørensen and T. Bruun, *Acta Chem. Scand.*, 1947, **1**, 112.

⁴⁵ *J.*, 1940, 683.

⁴⁶ S. Keimatsu, T. Ishiguro, and G. Fukuri, *J. Pharm. Soc. Japan*, 1937, **57**, 69.

⁴⁷ J. R. Hosking and C. W. Brandt, *Ber.*, 1935, **68**, 1313.

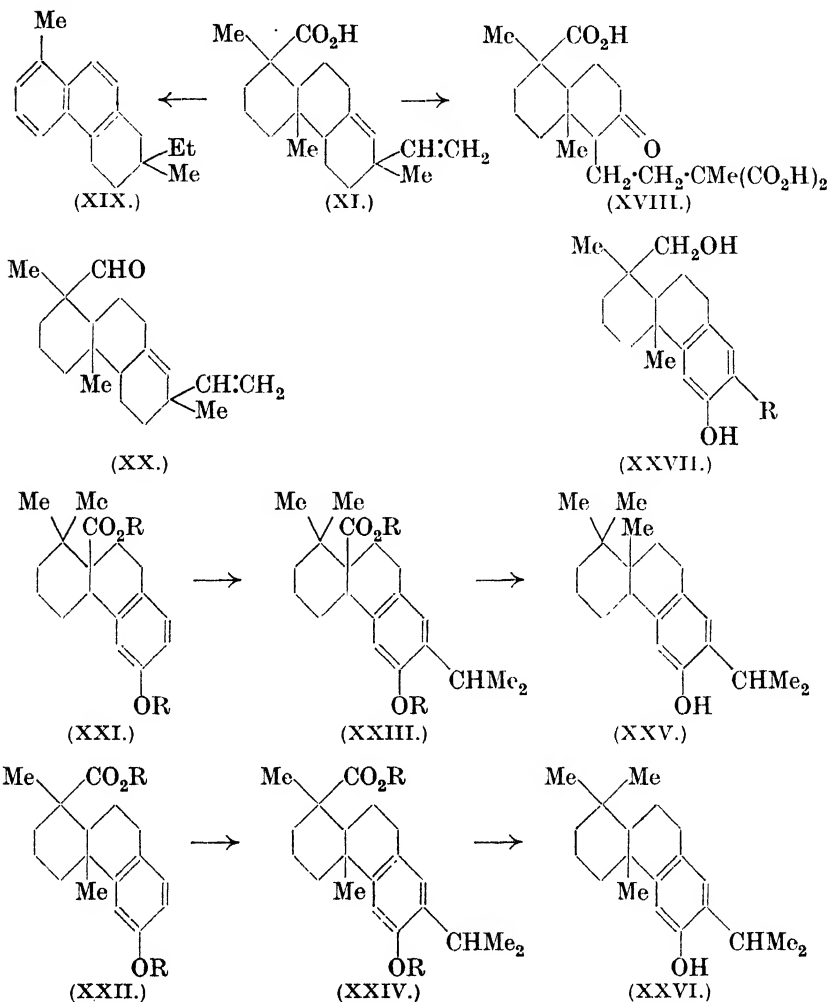
⁴⁸ J. R. Hosking, *New Zealand J. Sci. Tech.*, 1937, **19**, 208.

⁴⁹ *J.*, 1938, 1006.

⁵⁰ H. Plimmer, W. F. Short, and P. Hill, *ibid.*, p. 694.

⁵¹ *J. Amer. Chem. Soc.*, 1939, **61**, 2528.

to 6-hydroxydehydroabietic acid (XXIV; R = H) prepared by them. W. P. Campbell and D. Todd⁵² attempted to distinguish between these



structures by converting methyl *O*-methylpodocarpate (XXI or XXII; R = Me) into the 7-acetyl derivative by Friedel-Crafts condensation, treating this ketone with methylmagnesium iodide, dehydrating the carbinol, and reducing the isopropenyl group to give methyl *O*-methyl-7-isopropylpodocarpate (XXIII or XXIV; R = Me). It was not identical with methyl 6-methoxydehydroabietate (XXIV; R = Me), but this fails to eliminate (XXII; R = H) for podocarpic acid as the difference might lie in the configurations of C_1 , C_{11} , or C_{12} . Subsequently, W. P. Campbell and D. Todd⁵³

⁵² *J. Amer. Chem. Soc.*, 1940, **62**, 1287.

⁵³ *Ibid.*, 1942, **64**, 928.

eliminated the asymmetry at C_1 by reducing to methyl the carboxyl group of 7-isopropylpodocarpic and 6-hydroxydehydroabietic acids by the stages: $\cdot\text{CO}_2\text{H} \longrightarrow \cdot\text{COCl} \longrightarrow \cdot\text{CHO} \longrightarrow \cdot\text{CH}\cdot\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2 \longrightarrow \cdot\text{Me}$, to give the same 6-hydroxydehydroabietane (XXVI). This excludes (XXV) and hence (XXI), but the alternative to (XXII) with the C_1 - CO_2H and C_{12} -Me interchanged is still possible. 6-Hydroxydehydroabietane also proved to be identical with the resinol, ferruginol, isolated previously by C. W. Brandt and L. G. Neubauer.⁵⁴ Reduction of *O*-methylpodocarpic acid to the primary alcohol, *O*-methylpodocarpinol, by the steps $\cdot\text{CO}_2\text{H} \longrightarrow \cdot\text{COCl} \longrightarrow \cdot\text{CHO} \longrightarrow \cdot\text{CH}_2\cdot\text{OH}$,⁵³ or directly with lithium aluminium hydride,⁵⁵ followed by dehydration and dehydrogenation, yielded 6-methoxy-1-ethylphenanthrene. This clearly involves a Wagner-Meerwein rearrangement on dehydration of the carbinol, and therefore establishes (XXII; $R = H$) as the structure of podocarpic acid. Furthermore, podocarpic and abietic acids have the same configurations at C_{11} and C_{12} , but differ in that of C_1 . Acids of this structure have been synthesised,⁵⁶ but comparison with podocarpic acid awaits resolution of the synthetic acids.

L. F. Fieser and W. P. Campbell⁵¹ showed that 6-hydroxydehydroabietinol (XXVII; $R = \text{CHMe}_2$) exhibits marked oestrogenic activity, while C. W. Brandt and D. J. Ross⁵⁷ have recently shown that podocarpinol (XXVII; $R = H$) is similarly active. The latter prepared podocarpinol by Rosenmund reduction of the acid chloride of *O*-acetylpodocarpic acid, followed by copper chromite hydrogenation, whereas H. H. Zeiss *et al.*⁵⁵ prepared it by direct lithium aluminium hydride reduction of podocarpic acid.

Now that the structures of many of the resin acids and related diterpenes have been elucidated, attention has been turned to their stereochemistry, *i.e.*, the configurations of C_1 , C_7 , C_{11} , C_{12} , C_{13} , and C_{14} . The configurations of C_1 , C_{11} , and C_{12} hinge on the tricarboxylic acid, $C_{11}\text{H}_{16}\text{O}_6$, obtained on permanganate oxidation of abietic and pimaric acids.³⁶ This tricarboxylic acid is optically inactive, and must possess either of the *meso*-structures (XXVIIIa or b). Inasmuch as abietic acid is converted into dehydroabietic acid under conditions such that C_1 , C_{11} , and C_{12} take no part, dehydroabietic acid must possess either structure (VIa) or (VIb). Now Campbell and Todd⁵³ have shown that 6-hydroxyabietic acid differs from podocarpic acid (apart from the *isopropyl* group at C_7) in having the opposite configuration at C_1 , *i.e.*, if dehydroabietic acid is (VIa), then podocarpic acid is (XXIIa) and *vice versa* (VIb and XXIIb). Arguing from Stuart models Campbell and Todd deduced that the carboxyl group is more sterically hindered in (VIa) than in (XXIIa), whereas this is reversed for (VIb) and

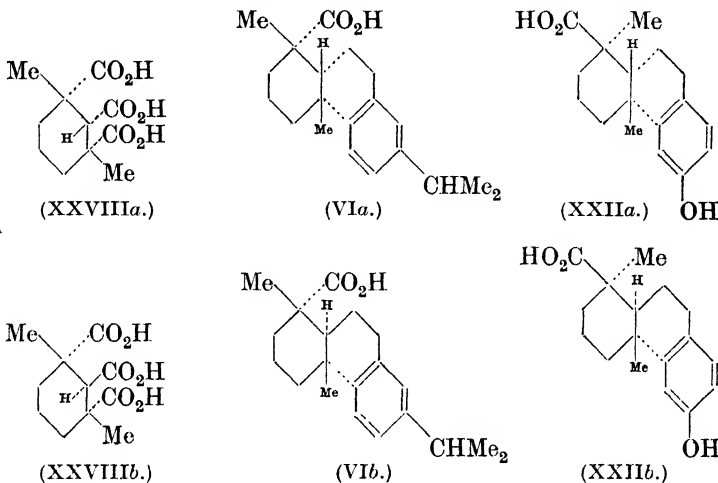
⁵⁴ *J.*, 1939, 1031.

⁵⁵ H. H. Zeiss, C. E. Slimowicz, and V. Z. Pasternak, *J. Amer. Chem. Soc.*, 1948, 70, 1981.

⁵⁶ B. K. Bhattacharya, *J. Indian Chem. Soc.*, 1945, 22, 165; R. D. Haworth and B. P. Moore, *J.*, 1946, 633.

⁵⁷ *Nature*, 1948, 161, 892.

(XXIIb). As the carboxyl group of podocarpic acid is much more resistant to esterification and hydrolysis than that of dehydroabietic acid, it was concluded that dehydroabietic acid is (VIb) and podocarpic acid (XXIIb). The greater steric hindrance of the carboxyl group of podocarpic acid is further exemplified in that, whereas methyl dehydroabietate and methyl 6-methoxydehydroabietate give diphenylcarbinols,⁵⁸ methyl *O*-methyl-podocarpate fails to react with phenylmagnesium bromide.⁴⁹



Arguments of this type, from the study of models of *cis*-decalin having the conventional Sachse-Mohr two-boat configuration, can hardly be regarded as a rigid proof. Moreover, it has recently been re-emphasised that the two-chair configuration of *cis*-decalin is at least as stable as, if not more stable than, the two-boat configuration.⁵⁹ Whereas on the arguments of Campbell and Todd the tricarboxylic acid would be (XXVIIIb) and rings A/B *trans*-fused, R. Lombard⁶⁰ has reached the opposite conclusion. Treatment of the tricarboxylic acid with acetyl chloride furnishes a mixture of two anhydrides, m.p.s *ca.* 100° and 170–172°, reconverted into the parent acid on hydrolysis. D. H. R. Barton and G. A. Schmeidler⁶¹ argue on symmetry grounds that the higher-melting anhydride is the 1 : 12-anhydride and the lower melting the 1 : 11(or 11 : 12)-anhydride. Lombard⁶⁰ found that the action of heat alone at 250° on the tricarboxylic acid yielded the higher-melting anhydride, which he considered to be the 1 : 11(or 11 : 12)-anhydride, and therefore C₁₁ and C₁₂ are *cis*. However, if in fact this is the 1 : 12-anhydride then neither experiment throws any light on the configuration of C₁₁. Barton and Schmeidler⁶¹ have made a new approach

⁵⁸ H. H. Zeiss, *J. Amer. Chem. Soc.*, 1947, **69**, 302; 1948, **70**, 858.

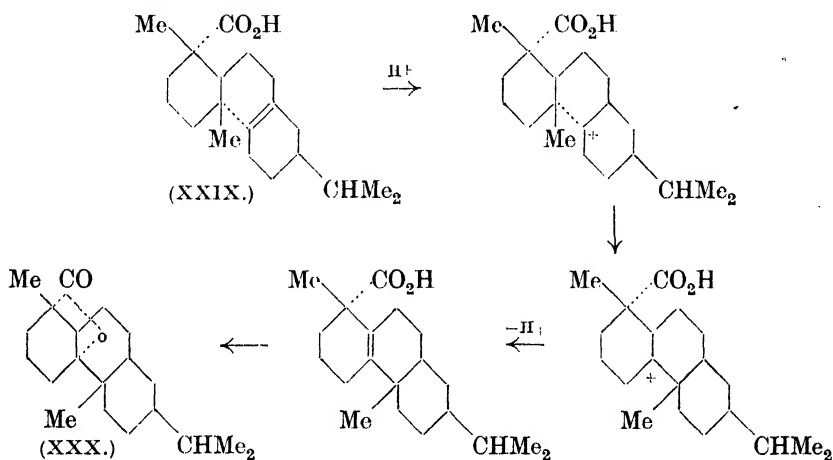
⁵⁹ O. Bastiansen and O. Hassel, *Tids. Kjemt.*, 1943, **3**, 91; *Nature*, 1946, **157**, 765; D. H. R. Barton, *J.*, 1948, 340.

⁶⁰ Thesis, Paris, 1943, p. 43; *Bull. Soc. chim.*, 1946, **13**, 428.

⁶¹ *J.*, 1948, 1197.

to this problem by utilising the dissociation constants of the tricarboxylic acid and analogous polycarboxylic acids in a method of electrostatic-energy differences, and conclude that C_{11} has the *trans*-configuration. Hence abietic, pimaric, and related resin acids have the same configurations at C_1 , C_{11} , and C_{12} as in (VIb), with *trans*-fusion of rings A/B.

More recently D. H. R. Barton⁶² has concluded from models that the *trans*-fusion of rings A/B prevents lactonisation of the C_1 -carboxyl on C_{13} . This conclusion throws doubt on the structures assigned earlier to the lactones from dihydroabietic and dihydropimaric acids (cf. IX). Barton therefore suggests that after the double bond reaches the 13:14-position a carbonium-ion rearrangement is induced by the strong acid in which the C_{12} -methyl moves to C_{13} with inversion at C_{12} , thus permitting γ -lactonisation on C_{12} ; *e.g.*, for a dihydroabietic acid:

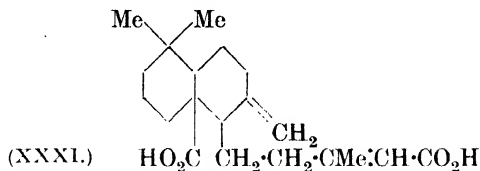


There is a close analogy for this scheme in the formation of Westphalen's diol from cholestane-3(β):5:6(β)-triol.

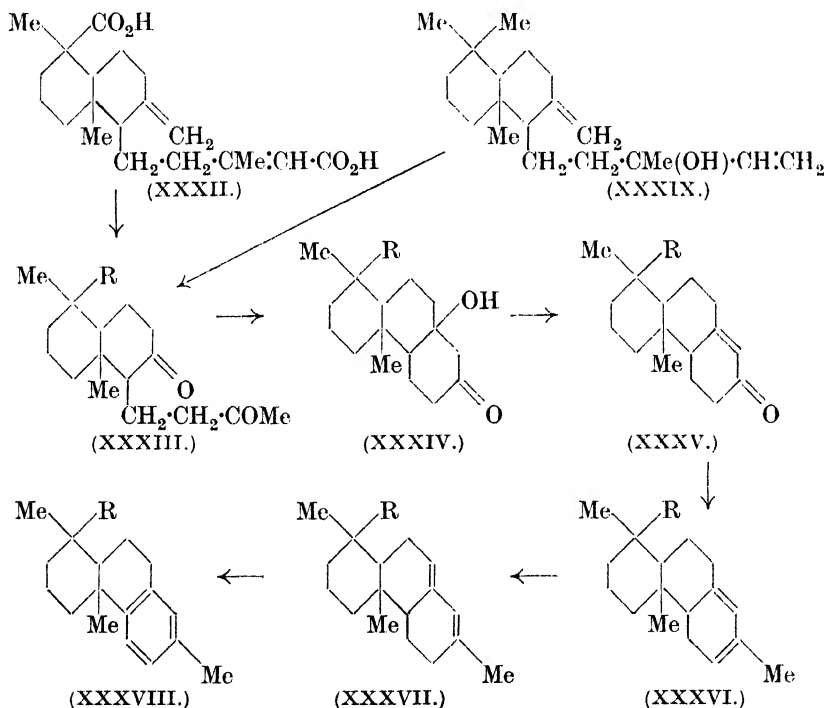
Early work of L. Ruzicka and his collaborators³⁸ on the dicarboxylic acid, agathic acid from Manila and Kauri copal, had indicated the dicyclic structure (XXXI). Formic acid converts agathic acid into the tricyclic *isoagathic* acid which is dehydrogenated to pimanthrene, and like agathic acid loses one carboxyl group above the melting point to give the nor-acid. One ester group of dimethyl agathate is readily hydrolysed and the product decarboxylated to methyl noragathate, the carbomethoxy-group of which resists hydrolysis as does the second ester group of dimethyl agathate and both the ester groups of dimethyl *isoagathate*. It was argued that the carboxyl group readily eliminated was that concerned in the cyclisation (the 8₂carboxyl group of *isoagathic* acid), while the other carboxyl group must occupy a hindered position, presumably different from that in abietic acid owing to their contrasting behaviour. The methyl group of position 12

⁶² *Chem. and Ind.*, 1948, 638.

and the carboxyl group of position 1 were therefore interchanged as in (XXXI). Subsequently, L. Ruzicka and H. Jacobs⁶³ located this carboxyl



group by reducing norisogathic acid to the primary alcohol, which after dehydration and dehydrogenation gave 7-methyl-1-ethylphenanthrene. This behaviour parallels that of abietic acid,³⁶ and it is evident that a Wagner-Meerwein rearrangement occurs on dehydration of the carbinol, and that the hindered carboxyl group is attached to carbon 1 as in (XXXII).

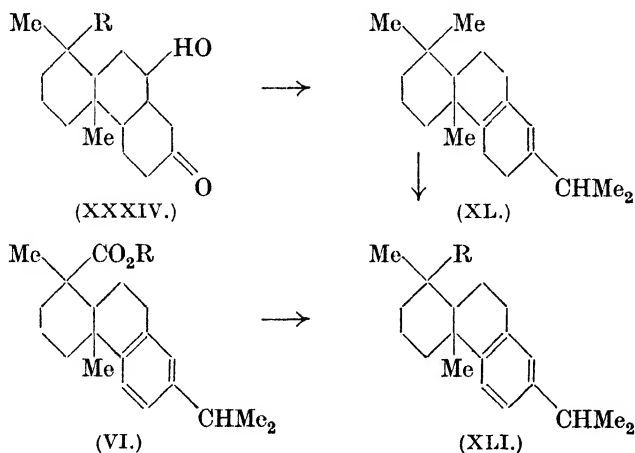


The diketo-ester (XXXIII; $\text{R} = \text{CO}_2\text{Me}$), obtained on ozonisation of dimethyl agathate (together with formaldehyde and oxalic acid), was cyclised by alkali to the β -hydroxy-ketone (XXXIV; $\text{R} = \text{CO}_2\text{Me}$), which dehydrated to the $\alpha\beta$ -unsaturated ketone (XXXV; $\text{R} = \text{CO}_2\text{Me}$). Treatment of this with methylmagnesium iodide and dehydration gave the diene ester (XXXVII; $\text{R} = \text{CO}_2\text{Me}$) (λ_{max} . 2380 \AA .), presumably by the isomeris-

⁶³ *Rec. Trav. chim.*, 1938, **57**, 509.

ation of (XXXVI; $R = \text{CO}_2\text{Me}$) analogous to the conversion of sapietic acid into abietic acid (λ_{max} , 2375 Å.). This diene ester was then partly dehydrogenated by palladium-charcoal,⁶⁴ or by the action of *N*-bromosuccinimide followed by dehydrobromination,⁶⁵ to (XXXVIII; $R = \text{CO}_2\text{H}$) analogous to dehydroabietic acid. L. Ruzicka, R. Zwicky, and O. Jeger⁶⁵ have now converted this acid by four steps ($\text{XXXVIII; } R = \text{CO}_2\text{H} \rightarrow \text{COCl} \rightarrow \text{CHO} \rightarrow \text{CH:N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2 \rightarrow \text{Me}$) into the tetramethylocta-hydrophenanthrene (XXXVIII; $R = \text{Me}$) which was also obtained from the diketone (XXXIII; $R = \text{Me}$) formed by ozonisation of manoöl (XXXIX)¹ through the stages (XXXIV, XXXV, XXXVI, XXXVII, and XXXVIII; $R = \text{Me}$). Agathic acid and manoöl therefore have the same configurations at C_{11} and C_{12} .

In an attempt to relate the stereochemistry of rings A and B of these substances to that of abietic acid, L. Ruzicka and E. Bernold⁶⁶ oxidised dimethyl agathate with permanganate and obtained an optically active monomethyl ester anhydride of a C_{11} -tricarboxylic acid, which resisted hydrolysis, and so prevented comparison with the optically inactive tricarboxylic acid (XXVIII) obtained from abietic acid.³⁶ More recently O. Jeger, O. Dürst, and G. Büchi⁶⁷ treated the hydroxy-ketone (XXXIV; $R = \text{Me}$) from manoöl with isopropylmagnesium bromide, followed by dehydration, to give the diene (XL). This was dehydrogenated, by successive



treatment with *N*-bromosuccinimide and sodium acetate, to the trimethyl isopropyloctahydrophenanthrene, dehydroabietane (XLI; $R = \text{Me}$), characterised as the 6:8-dinitro-derivative, which was also obtained from dehydroabietic acid (VI; $R = \text{H}$) through the successive steps (XLI; $R = \text{COCl} \rightarrow \text{CHO} \rightarrow \text{CH:N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2 \rightarrow \text{Me}$). The dicyclic diterpenes, sclareol,¹ manoyl oxide,¹ manoöl, and agathic acid, are all there-

⁶⁴ L. Ruzicka, E. Bernold, and A. Tallichet, *Helv. Chim. Acta.*, 1941, **24**, 223.

⁶⁵ *Ibid.*, 1948, **31**, 2143.

⁶⁶ *Ibid.*, 1941, **24**, 931.

⁶⁷ *Ibid.*, 1947, **30**, 1853.

fore correlated with abietic acid as having the same configurations at C_{11} and C_{12} , but agathic acid, like podocarpic acid, has the configuration of C_1 of abietic acid reversed.

Although this review of the diterpenes has been restricted to the resin acids, numerous hydrocarbons, alcohols, oxides, etc., have been studied during the past twelve years, but in no case has the structural investigation advanced far enough to warrant a report at this stage.

S. H. H.

5. COLCHICINE AND RELATED COMPOUNDS.

According to current views the chemistry of colchicine is closely associated with the chemistry of homocyclic 7-membered rings—more especially of the two unsaturated types, tropolone and dibenzcycloheptatriene. These views are still partly speculative, but growing interest in the several problems involved makes it opportune to review the subject at its present stage of development.

Tropolone and Stipitatic Acid.—M. J. S. Dewar¹ interpreted the puzzling chemical behaviour of stipitatic acid in terms of formula (VI), and proposed the name *tropolone* for the parent cycloheptatrienolone (I) to which certain significant properties were ascribed; later,² he suggested that the same type of ring system was also present in colchicine. At present neither tropolone nor any derivative of rigidly proved structure is known, and, in the absence of such reference compounds, the initial question concerns the adequacy of structure (I) to support the properties ascribed to it.

Dewar regards tropolone as an enol of pronounced acidic character, capable of alkylation or acylation on either oxygen atom (important in unsymmetrically *C*-substituted tropolones) and having potentialities for isomerisation to benzoic acid through benzilic rearrangement. Granting enolic stability,³ these properties will be conceded readily in view of the tautomeric possibilities of (I), and of appropriate part-analogies in the acidity of hydroxymethylene-ketones and in the benzilic change incidental to Wallach's degradation of diosphenols to cyclopentanone derivatives. Less easily assessable is the further postulate that resonance between (I) and (II),⁴ or between (III) and (IV),¹ confers on the molecule abnormal stability (pseudo-aromaticity) with masking of the ethylenic and carbonyl functions. In each pair the question of resonance is bound up with the question of the planar structure of the molecule, while calculation of the inter-oxygen distance⁴ shows that it is normally too large for strong hydrogen-chelation. On the other hand, resonance is not excluded from the puckered ring-system of cyclooctatetraene⁵ and there may be close analogy between the structure of tropolone and the stable structure of azulene (V).⁶ While, therefore, it must be left for synthesis and examin-

¹ *Nature*, 1945, 155, 50.

² *Ibid.*, p. 141.

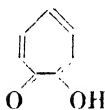
³ Compare G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, 1947, 30, 663.

⁴ M. J. S. Dewar, *Nature*, 1945, 155, 479.

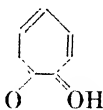
⁵ *Ann. Reports*, 1947, 44, 123.

⁶ *Ibid.*, 1947, 44, 162; W. Baker, Tilden Lecture, *J.*, 1945, 258.

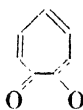
ation of a typical compound to decide the extent of resonance in tropolone and the degree of masking in particular functional groups, the concept is essentially feasible and its chief claim to present recognition is the aptness with which it interprets and correlates problems of structure presented by the chemistry of several natural products.



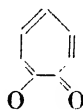
(I.)



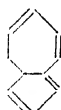
(II.)



(III.)



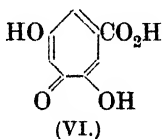
(IV.)



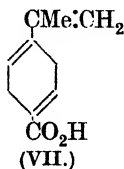
(V.)

Stipitatic acid, $C_8H_6O_5$, a cream-coloured metabolic product of *Penicillium stipitatum* Thom,⁷ has three active hydrogen atoms (Zerewitinoff), gives a deep red colour with ferric chloride, and behaves as a dibasic acid on titration, affording deep yellow solutions of the neutral disodium salt. The presence of one carboxyl group is shown by decarboxylation to a monobasic acid, $C_7H_6O_3$, which reproduces the colour reactions with ferric chloride and with alkali. Methylation of stipitatic acid with diazomethane produces two isomeric trimethyl derivatives, $C_7H_3O(OMe)_2(CO_2Me)$, which are insoluble in alkali, give no colour with ferric chloride, and, like the parent acid, are unresponsive to carbonyl reagents. Definite ketonic properties, however, appear in the reduction products of the acid although the course of reduction is apparently not simple. For instance, hydrogenation with platonic oxide as catalyst yields a mixture of neutral and acidic oils, each having ketonic reactions, and the latter affording the crystalline (mono-) 2:4-dinitrophenylhydrazone of a tetrahydrostipitatic acid. Oxidation of stipitatic acid proceeds too far for the results to be structurally significant, but the compound is stable to dissolution in concentrated hydrochloric or nitric acid, and, with bromine, substitution rather than addition occurs. When fused with alkali the acid is isomerised to 5-hydroxyisophthalic acid in high yield. For further details the original papers should be consulted,^{7, 1} but the summary given sufficiently indicates the acidic enolone characteristics with masked carbonyl and olefinic reactivity which, together with isomerisation to the benzenoid type, are interpreted by (VI) (or by the formula of the tautomeric enolone) and are difficult to account for otherwise.

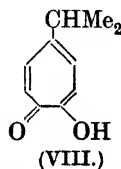
It has also been suggested⁴ that a second mould-product, namely puberulic acid,⁸ may be one of the three possible monohydroxystipitatic acids.



(VI.)



(VII.)



(VIII.)

⁷ J. H. Birkinshaw, A. R. Chambers, and B. Raistrick, *Biochem. J.*, 1942, **36**, 242.

⁸ J. H. Birkinshaw and B. Raistrick, *ibid.*, 1932, **26**, 441.

The Thujaplicin Group.—The heartwoods of red cedar (*Thuja plicata* Don.) from American and Swedish sources have afforded four compounds, $C_{10}H_{12}O_2$, of which one, namely dehydroperillic acid, has been assigned the structure (VII), based mainly on the results of ozonolysis and on its ready isomerisation to *p*-isopropylbenzoic acid.⁹ The remaining three isomers¹⁰ form a group of closely related compounds having enolic properties, very similar absorption spectra (maxima, 230–240 $m\mu$; broad absorptions, 320–370 $m\mu$), and a capacity in common to absorb four moles of hydrogen on catalytic hydrogenation. By the latter treatment two of these isomers yield oils, but the third, γ -thujaplicin, yields a crystalline diol, $C_{10}H_{20}O_2$, which is cleaved by periodic acid to a dialdehyde which can be oxidised to a dibasic acid. This acid must be γ -isopropylpimelic acid, since dry distillation of its barium salt affords a ketone which is identified as 4-isopropylcyclohexanone. Direct oxidation of γ -thujaplicin with chromic acid yields isobutyric acid. Formula (VIII) is accordingly proposed for γ -thujaplicin, and it is tentatively suggested that the other two isomers differ from it, and from each other, only in the location of the isopropyl substituent.*

Purpurogallin.—This compound, $C_{11}H_8O_5$, was first obtained in 1869¹¹ as an oxidation product of pyrogallol, and was later found, combined as glucosides, in the colouring matters of various galls.¹² Although its molecular formula was early established¹³ its structure has presented a puzzle of some persistence. Conveniently prepared by oxidising pyrogallol with sodium iodate,¹⁴ purpurogallin is a red crystalline compound which contains four hydroxyl groups and a masked carbonyl group. It yields substitution products with bromine and is stable at 150° to hydrogen chloride in ethanol. When strongly heated with concentrated alkali it affords an isomer, purpurogallone, together with an oxidation product of the latter, isopurpurogallone, $C_{22}H_{14}O_{10}$. Purpurogallone, as a trihydroxy-, easily lactonised carboxylic acid, which yields naphthalene when distilled with zinc dust, is probably correctly formulated as (IX),¹⁵ while for purpurogallin itself the earlier formulæ (X)¹⁶ and (XI)¹⁷ have now been replaced by the benzotropolone formula (XII).^{18, 19}

Extensive support for the structure (XII) is obtained from a study of

⁹ A. B. Anderson and E. C. Sherrard, *J. Amer. Chem. Soc.*, 1933, **55**, 3813.

¹⁰ H. Erdtman and J. Gripenberg, *Nature*, 1948, **161**, 719.

¹¹ A. Girard, *Ber.*, 1869, **2**, 562.

¹² M. Nierenstein, *J.*, 1919, **115**, 1328; M. Nierenstein and A. Swanton, *Biochem. J.*, 1944, **38**, 373.

¹³ A. G. Perkin and A. B. Steven, *J.*, 1903, **83**, 192.

¹⁴ T. W. Evans and W. M. Dehn, *J. Amer. Chem. Soc.*, 1930, **52**, 3647.

¹⁵ A. G. Perkin, *J.*, 1912, **101**, 808.

¹⁶ R. Willstätter and H. Heiss, *Annalen*, 1923, **433**, 17.

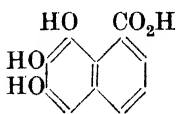
¹⁷ H. F. Dean and M. Nierenstein, *Ber.*, 1913, **46**, 3868.

¹⁸ J. A. Barltrop and J. S. Nicholson, *J.*, 1948, 116.

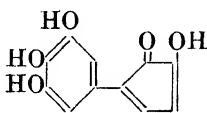
¹⁹ R. D. Haworth, B. P. Moore, and P. L. Pauson, *J.*, 1948, 1045.

* H. Erdtman and J. Gripenberg, *Acta Chem. Scand.*, 1948, **2**, 625, give experimental details relating to the structure of γ -thujaplicin and provide evidence (*ibid.*, p. 639) that α -thujaplicin is the vicinally substituted isomer, *viz.*, α -isopropyltropolone.

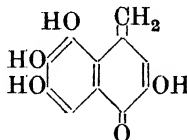
the methylation products of purpurogallin of which mono-, di-, tri-, and tetra-methyl ethers are known : ^{16, 18, 19, 20} all are unresponsive to carbonyl



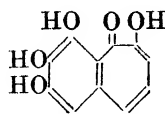
(IX.)



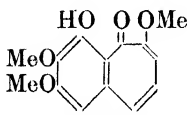
(X.)



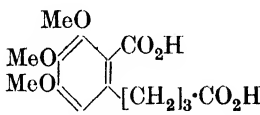
(XI.)



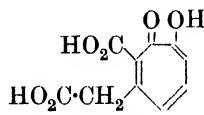
(XII.)



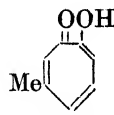
(XIII.)



(XIV.)



(XV.)



(XVI.)

reagents. The trimethyl ether, formulated as (XIII), is only feebly acidic ²⁰ and is hydrogenated (a) with Raney nickel as catalyst ¹⁸ to a hexahydride which is a phenol and not an α -diol, or (b) with platinum oxide as catalyst ¹⁹ to a mixture of products from which, by Girard's reagent-T, a ketonic tetrahydride has been isolated. The tetramethyl ether, which can exchange one unspecified methoxyl for an ethoxyl group, ²⁰ or undergo hydrolysis to (XIII), ¹⁹ is oxidised by permanganate to 3 : 4 : 5-trimethoxyphthalic acid ¹⁸ and by alkaline hydrogen peroxide to (XIV), which has been synthesised. ¹⁹

Interesting possibilities emerge from the results of oxidising purpurogallin by air in presence of alkali. ¹⁹ The process apparently causes degradation of the pyrogallol nucleus, and the tribasic acid so produced is tentatively regarded as (XV), which by decarboxylation yields the monobasic acid (XVI). Both of these products show tropolone characteristics, and the suggestion has been made that compounds of the γ -thujaplicin type arise in Nature from substituted pyrogallols by successive formation and degradation of purpurogallin analogues. The mechanism of purpurogallin formation is still in the speculative stage, ^{16, 19} but it must ultimately accommodate the facts that by suitable oxidation (a) gallic acid yields purpurogallincarboxylic acid ($C_{11}H_7O_5 \cdot CO_2H$), ^{16, 21} (b) 2 : 3-dihydroxyanisole, in presence of pyrogallol, yields a purpurogallin monomethyl ether but, alone, does not afford an analogous product. ¹⁶

Colchicine.—The extent of scientific interest in the alkaloid, colchicine, is reflected in a formidable bibliography, and a compilation ²² made in 1946 lists some 1300 papers. These are mostly concerned with the biological effects of colchicine, which derive from its capacity to arrest cell division at the early metaphase, and which make it a valuable aid in cytological studies, in the artificial production of polyploid varieties of plants and animals, in the biological assay of hormones and, to some extent also, in tumour

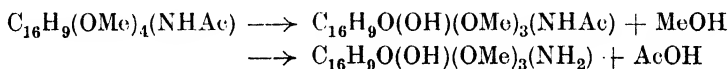
²⁰ J. Herzig, *Annalen*, 1923, **432**, 99.

²¹ A. G. Perkin and F. M. Perkin, *J.*, 1908, **93**, 1186.

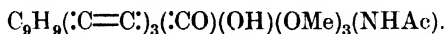
²² O. J. Eigsti and P. Dustin, *Lloydia*, 1947, **10**, 65.

therapy. This intensification of biological interest during the past twelve years has redirected attention to the chemistry of the alkaloid. As briefly discussed in an earlier Report,²³ A. Windaus in 1924 proposed for colchicine the formula (XVII), or, alternatively, the variant in which the methoxymethylene and carbonyl groups are interchanged. Recent work, however, has shown the need for revision, and in the present Report a comprehensive survey of the degradative evidence is linked with current views on the structural problems involved.

Of the six oxygen atoms present in the molecule of colchicine, $C_{22}H_{25}O_6N$, five are accounted for by four methoxyl groups and an acetylated primary amino-group: the sixth is not immediately identifiable. One of the methoxyl groups is sharply differentiated from the others by the ease with which it is hydrolysed, the product of hydrolysis being colchiceine. Further hydrolysis causes deacetylation, and affords the so-called trimethylcolchicin acid:²⁵



Each of these products is acidic, but the first assumption that this is due to a carboxylic group proved to be inadequate, and the presence of a tautomeric enolone system is inferred from the following facts. (a) Both hydrolysis products differ from colchicine in giving intense colour reactions with ferric chloride. (b) Methylation of colchiceine affords two readily hydrolysable *O*-methyl ethers, *viz.*, colchiceine and *isocolchiceine*.^{26, 27} A similar pair of *O*-derivatives appears to result from the action of benzenesulphonyl chloride on trimethylcolchicin acid, two bisbenzenesulphonyl derivatives being formed, each of which yields the same *N*-benzenesulphonyl derivative on partial hydrolysis.²⁸ (c) Neither colchiceine nor colchicine itself reacts with the usual carbonyl reagents, but by catalytic hydrogenation each affords a hexahydride in which a new hydroxylic function appears, hexahydrocolchiceine being a diol, hexahydrocolchicine a mono-alcohol.²⁹ Allowing for reduction of a masked carbonyl group, the hydrogenation results show the presence of two olefinic groups, while a third olefinic group, which survives hydrogenation, is revealed in the formation of an oxide, $C_{22}H_{31}O_7N$, from hexahydrocolchicine in reaction with perbenzoic acid. The functional groups are summed up in the partial formula for colchiceine:



²³ *Ann. Reports*, 1938, **35**, 326.

²⁴ *Annalen*, 1924, **439**, 59.

²⁵ S. Zeisel, *Monatsh.*, 1885, **6**, 989; 1888, **9**, 1; S. Johnny and S. Zeisel, *ibid.*, 1888, **9**, 866.

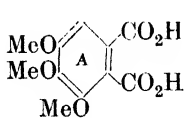
²⁶ K. Meyer and T. Reichstein, *Pharm. Acta Helv.*, 1944, **19**, 127.

²⁷ M. Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246.

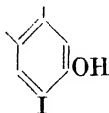
²⁸ A. Windaus, *Sitzungsber. Heidelberg. Akad. Wiss., Math.-Nat. Kl., A*, 1911, 2 Abh.

²⁹ K. Bursian, *Ber.*, 1938, **71**, 245.

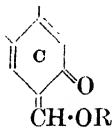
It may be concluded that colchiceine contains one aromatic ring—ring A—since it is oxidised by alkaline permanganate to 3 : 4 : 5-trimethoxyphthalic acid (XVIII).^{30, 31} The above partial formula therefore corresponds to the fully hydrogenated hydrocarbon $C_{16}H_{28}$, and in consequence colchiceine must be tricyclic.



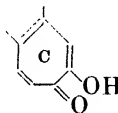
(XVIII.)



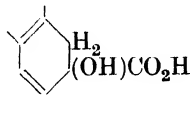
(XIX.)



(XX.)

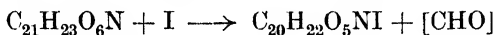


(XXI.)



(XXII.)

When colchiceine is treated with iodine in presence of alkali a second ring—ring C—becomes aromatic,^{31, 32} and the character of the absorption spectrum, similar in colchicine and colchiceine, changes markedly.^{29, 31} The process, which may be represented formally as :



causes the enolone properties to disappear, and the product, *N*-acetyliodo-colchinal, contains the phenolic structure (XIX) since oxidation of the derived methyl ether yields 4-iodo-5-methoxyphthalic acid.^{32, 34} The formyl group of *o*-hydroxy-benzaldehydes is similarly replaceable by iodine, and Windaus attempted to make this an analogy, and at the same time to express the enolone properties of colchiceine, by formulating ring C as the hydroxymethylene form (XX; $R = H$) of a substituted salicylaldehyde.²⁴ On this basis colchicine and isocolchicine would be the two stereoisomeric ethers (XX; $R = Me$). The stability thus attributed to the hydroxymethylene, over the usual aromatic form, is, however, anomalous, and this difficulty is avoided in the tropolone formula (XXI) for ring C, proposed by M. J. S. Dewar.² Thereby the duplication of *O*-derivatives is interpreted as structural isomerism, while conversion into (XIX) may be envisaged as the result of benzilic change to an intermediate (XXII) followed by oxidation and iodination. Dehydration of the same intermediate would afford a derivative of benzoic acid, and it is significant that colchicine, when heated with sodium methoxide in methanol, does yield a carboxylic acid which is isomeric with colchiceine and yields trimellitic acid (benzene-1 : 2 : 4-tricarboxylic acid) on oxidation.^{35, 36} It also follows from the tropolone formula (XXI) that hexahydrocolchiceine should be an α -diol, and there is evidence that the compound is cleaved by lead tetra-acetate⁴ or periodic acid.³⁷ Although the scission products are not well defined,

³⁰ A. Windaus, *Sitzungsber. Heidelberg. Akad. Wiss., Math.-Nat. Kl.*, A, 1910, 2 Abh.

³¹ *Idem, ibid.*, 1914, 18 Abh.

³² *Idem, ibid.*, 1919, 16 Abh.

³³ A. Cohen, J. W. Cook, and E. M. F. Roe, *J.*, 1940, 194.

³⁴ R. Grewe, *Ber.*, 1938, 71, 907.

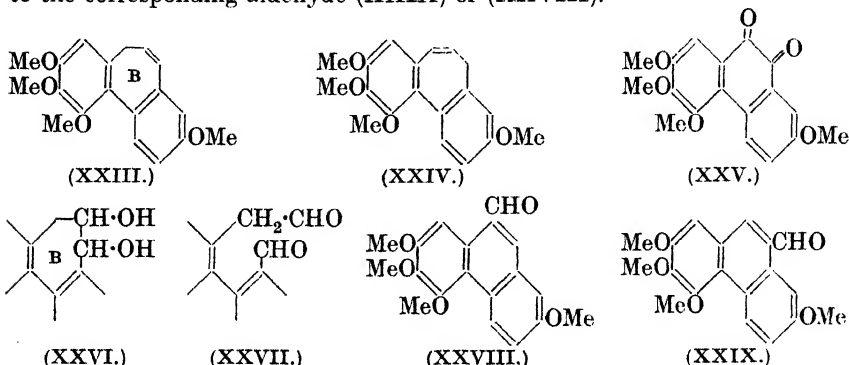
³⁵ Compare H. Lettré, *Angew. Chem.*, 1947, 59, A, 218.

³⁶ F. Šantavý, *Helv. Chim. Acta*, 1948, 31, 821.

³⁷ H. R. V. Arnstein, D. S. Tarbell, H. T. Huang, and G. P. Scott, *J. Amer. Chem. Soc.*, 1948, 70, 1669.

those from the latter reaction afford an amorphous 2:4-dinitrophenyl-hydrazone, which is apparently derived from a mono-aldehyde formed by internal condensation of the initial cleavage product.

Evidence for the nature of ring B, and a considerable insight into the general structure, are obtained from further degradation of *N*-acetyliodo-colchicol methyl ether. Dehalogenation yields *N*-acetylcolchicol methyl ether,³² which can be deaminated in several ways, *e.g.*: (i) directly, with elimination of acetamide, by treatment with phosphoric oxide in boiling xylene;^{38, 39} (ii) *via* the parent amine by (a) reaction with nitrous acid and dehydration of the resulting carbinol^{33, 39} or (b) Hofmann degradation.²⁴ Deaminocolchicol methyl ether (XXIII) is produced in each case and is accompanied in (i) and (iia) by an isomeride, *isodeaminocolchicol* methyl ether (XXIV). The structures assigned to these products are firmly established.³⁹ Each isomeride affords the same dihydride on hydrogenation, while oxidation of (XXIII) with sodium dichromate in acetic acid yields the phenanthraquinone (XXV); this has been synthesised, thereby establishing the presence and methoxylation pattern of the bridged diphenyl system. An unsaturated ketone, $C_{19}H_{18}O_5$, isolated as by-product of this oxidation, has been identified as described on p. 198. The nature of the three-carbon bridge is shown by the results of stepwise oxidation. With osmium tetroxide (XXIII) yields the glycol (XXVI), and this is cleaved by tetra-acetate, the intermediate dialdehyde (XXVII) undergoing cyclisation to the 10-phenanthraldehyde (XXVIII), which, by further oxidation, yields the corresponding 10-carboxylic acid. Similar stepwise oxidation of (XXIV) yields the 9-phenanthraldehyde (XXIX). The significant phenanthrene derivatives were synthesised on the usual Pschorr lines from appropriate *o*-nitrobenzaldehydes and phenylacetic acids to give 2:3:4:7-tetramethoxyphenanthrene-9- and -10-carboxylic acids. Each of these was oxidised to (XXV) and was reduced, *via* the benzenesulphonylhydrazide, to the corresponding aldehyde (XXIX) or (XXVIII).^{39, 40, 41}



³⁸ J. W. Cook and W. Graham, *J.*, 1944, 322.

³⁹ N. Barton, J. W. Cook, and J. D. Loudon, *J.*, 1945, 176.

⁴⁰ G. L. Buchanan, J. W. Cook, and J. D. Loudon, *J.*, 1944, 325.

⁴¹ J. MacMillan, Ph.D. Thesis, Glasgow, 1948.

Confirmatory evidence of the dibenzcycloheptatriene structure as in (XXIII) or (XXIV) is obtained from degradation of an iododeaminocolchinel methyl ether.⁴² This compound, prepared by elimination of acetamide from *N*-acetyliodocolchinel methyl ether, is oxidised by permanganate, without loss of carbon, to a dibasic acid which must be a homodiphenic acid, since its ester undergoes the Dieckmann reaction to form a derivative of phenanthrol.

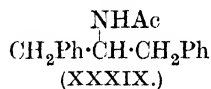
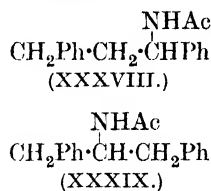
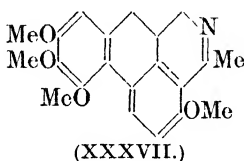
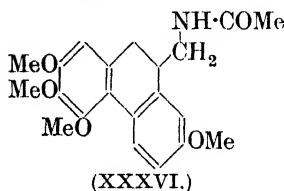
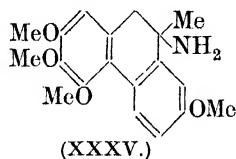
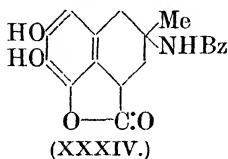
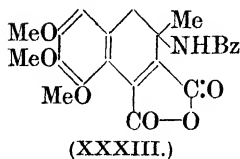
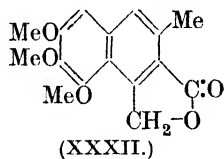
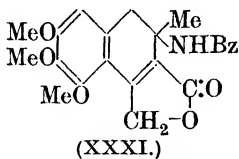
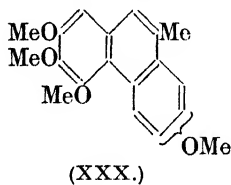
The implication that ring B may be 7-membered in colchicine itself brings under review the evidence on which A. Windaus²⁴ assigned the 6-membered structure and orientation shown in formula (XVII). (a) When heated with hydriodic acid and then distilled with zinc, deaminocolchinel methyl ether affords 9-methylphenanthrene of which, accordingly, it was regarded as a tetramethoxy-derivative, *viz.* (XXX). This conclusion has been refuted by synthesis of the two compounds (XXX),⁴⁰ neither of which is identical with deaminocolchinel methyl ether, and it is now known that the dibenzcycloheptatriene framework of this compound becomes rearranged to the methylphenanthrene type under the conditions of demethoxylation (p. 197). (b) Oxidation of colchinel methyl ether to 4-methoxyphthalimide suggests that the carbon atom which carries the amino-group in ring B is directly attached to ring C. (c) Oxidation of colchicine with chromic acid to a ketone, oxycolchicine, $C_{22}H_{23}O_7N$, requires the presence of an oxidisable methylene group which could be provided only in ring B. These two items are equally well accommodated in a 7-membered ring B, as shown in (XI), wherein the juxtaposition of methylene groups can also explain the otherwise perplexing presence of succinic acid among the oxidation products of colchicine and its derivatives.³¹ (d) The *N*-benzoyl derivative of trimethylcolchicinic acid is oxidised, with degradation of ring C, by cold alkaline permanganate to *N*-benzoylcolchide and to *N*-benzoylcolchicinic acid anhydride.²⁸ These were provisionally formulated²⁴ as (XXXI) and (XXXIII) respectively, since ready deamination of the former was consistent with aromatisation to a naphthalene derivative, *e.g.*, (XXXII), while treatment of the anhydride with hydriodic acid (involving demethylation, reduction, and partial decarboxylation) afforded a lactone, supposedly *peri*-linked as in (XXXIV). The evidence is too slight to establish these conclusions on an independent basis, and further investigation will be necessary to decide whether the ring-structure of the compounds* has significance in modifying the implications of the dibenzcycloheptatriene derivatives with respect to the nature of ring B in colchicine.

As was first pointed out by A. Cohen, J. W. Cook, and E. M. F. Roe,³³ the Windaus formula (XXXV) for colchinel methyl ether implies a readiness to eliminate ammonia which is not found in fact. The acetylated amine (XXXVI), representing a possible alternative structure, has been synthe-

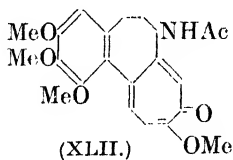
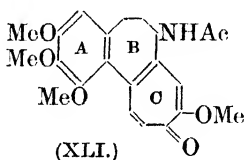
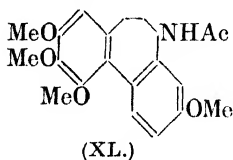
⁴² D. S. Tarbell, H. R. Frank, and P. E. Fanta, *J. Amer. Chem. Soc.*, 1946, **68**, 502.

* The results of unpublished work on these compounds, by J. W. Cook, T. Y. Johnston, and J. D. Loudon, make a naphthalene framework improbable and suggest, although they do not prove, the presence of a 7-membered ring.

ised,⁴³ and, in contrast with the deamination of *N*-acetylcolchinel methyl ether, is converted into the dihydroisoquinoline (XXXVII) by phosphoric



oxide in boiling xylene. It is of interest also that, by this treatment, the acetylated diphenylpropylamines (XXXVIII) and (XXXIX) yield 1 : 3-diphenylpropene, accompanied in the case of (XXXIX) by the corresponding dihydroisoquinoline. Since, further, Hofmann degradation is generally free from complications involving change in the carbon structure,⁴⁴ it is highly probable that ring B of colchinel methyl ether is 7-membered as in the derived deamino-compound (XXIII).



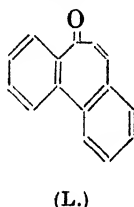
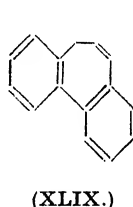
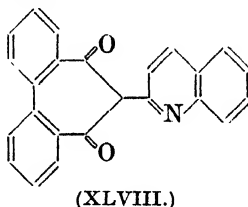
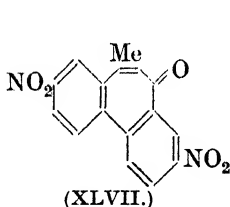
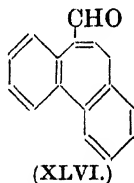
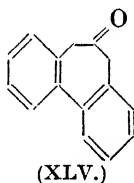
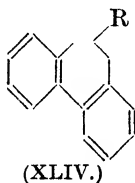
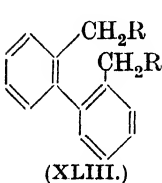
Accordingly, the balance of evidence suggests (XL) as the probable formula for *N*-acetylcolchinel methyl ether, and the formation of *iso*-deaminocolchinel methyl ether (XXIV), in course of deamination, is regarded as the result of prototropy in the triad system of (XXIII) and (XXIV) : confirmation of the position occupied by the acetamido-group is still, however, desirable. On the basis of this formula the considerations discussed in connection with ring C lead to (XLI) and (XLII) for colchicine and *isocolchicine*, not necessarily respectively. Doubtless these plausible, if rather unusual, conclusions will be tested thoroughly by future developments for which, already, fresh starting points are provided in the isolated

⁴³ J. W. Cook, G. T. Dickson, D. Ellis, and J. D. Loudon, in the press.

⁴⁴ P. G. Stevens and J. H. Richmond, *J. Amer. Chem. Soc.*, 1941, **63**, 3132.

observations that colchicine is isomerised by irradiation to lumicolchicine of which little is yet known;⁴⁵ that colchicine is oxidised by periodic acid to a monocarboxylic acid, $C_{21}H_{23}O_6N$, which may well represent an early stage in the degradation of ring C;²⁶ and that the oxygenated lateral rings of *N*-acetylcolchicinol are both degraded, in preference to ring B, by means of perbenzoic acid.⁴⁶

Dibenzcyclohepta-1:3:5-trienes and -3:5-dienes.—Apart from the degradation products of colchicine, the known compounds of these types are all obtained by synthesis which is usually effected by the interaction of suitable *oo'*-side-chains carried in symmetrically substituted diphenyls. In this way,⁴⁷ from *oo'*-dibromo-*oo'*-ditolyl (XLIII; R = Br) by condensation with malonic ester followed by hydrolysis and elimination of carbon dioxide, the carboxylic acid (XLIV; R = CO₂H) has been obtained, and is converted by the Curtius reaction into the amine (XLV; R = NH₂). The same amine is also produced by reducing the oxime of the ketone (XLV), which is formed through cyclisation of the dinitrile (XLIII; R = R = CN) by Thorpe's method, or of the diester (XLIII; R = CO₂Et) by the Dieckmann reaction, and hydrolysis of the products.^{47, 48} Further variants of the synthesis are the cyclisation, under hydrolytic treatment, of the diacetal [XLIII; R = CH(OEt)₂] to the aldehyde (XLVI)⁴⁹ and the direct formation of the ketone (XLVII) by heating 2-bromo-5-nitroacetophenone with copper.⁵⁰ The condensation of diphenic anhydride with



quinaldine is probably also of the same general type, the feebly acidic product being formulated as quinodiphenone (XLVIII).^{51, 52} Many of

⁴⁵ R. Grewe, *Naturwiss.*, 1946, 187.

⁴⁶ H. Fernholz, *Angew. Chem.*, 1948, 60, A, 62.

⁴⁷ J. Kenner and E. G. Turner, *J.*, 1911, 99, 2101; J. Kenner, *J.*, 1913, 103, 613.

⁴⁸ J. W. Cook, G. T. Dickson, and J. D. Loudon, *J.*, 1947, 746.

⁴⁹ R. Weitzenböck, *Monatsh.*, 1913, 34, 199.

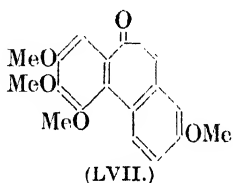
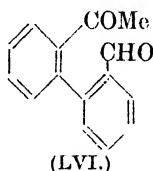
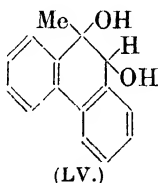
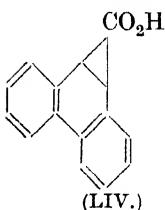
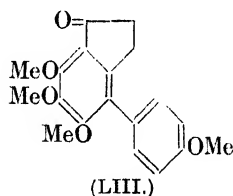
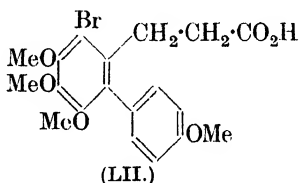
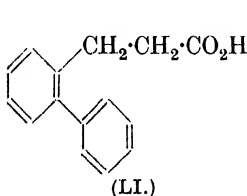
⁵⁰ W. Borsche and A. Herbert, *Annalen*, 1941, 546, 293.

⁵¹ A. Taurin, *J. pr. Chem.*, 1939, 153, 177.

⁵² F. Bell and F. Briggs, *J.*, 1941, 282.

these reactions which bridge the diphenyl system occur with great ease, and the carbon framework of the products shows little tendency to rearrange except under drastic treatment.

The parent triene (LXIX) is formed from the acetamido-compound (XLIV; $R = \text{NHAc}$) by the action of phosphoric oxide in boiling xylene.⁴⁸ It is readily hydrogenated to the dihydride (XIV; $R = \text{H}$) and is oxidised with sodium dichromate in acetic acid to a mixture of phenanthraquinone and the trienone (L), the latter being best prepared with selenium dioxide as oxidising agent. It should also be possible to prepare the trienolone of the series (dibenztropolone) for comparison with tropolone behaviour. Stepwise oxidation of the triene with osmium tetroxide and lead tetraacetate leads to 9-phenanthraldehyde, and the parallelism with deaminocolchinal methyl ether is further extended by the fact that, like the latter, the triene affords 9-methylphenanthrene when heated with hydriodic acid and then distilled with zinc. 9-Methylphenanthrene is also formed, together with the triene, by destructive distillation of the hydrochloride (XLIV; $R = \text{NH}_2\cdot\text{HCl}$). Oxidation to phenanthraquinone has been observed with the compounds (XLV), (XLVI), (XLIX), (L) and with the dihydride of (L), and may have some diagnostic value in the series.^{41, 48, 49}



Obvious complications arise when the lateral rings are unsymmetrically substituted. Tautomerism in such dibenzcycloheptatrienes has not been studied, but the individual stability of deaminocolchinal methyl ether (XXIII) and its isomeride (XXIV) recalls the reluctant propotropy of 1 : 3-diarylpropenes⁵³ rather than the mobility of the triad system in indene. The primary consideration is that of synthesis which is faced with the comparative inaccessibility of suitable, unsymmetrically substituted diphenyls. Model experiments show that Friedel-Crafts cyclisation of the diphenylpropionic acid (LI) takes the expected course, yielding mainly the indanone, although a much smaller proportion of the dibenzcyclohepta-

⁵³ C. K. Ingold and H. A. Piggott, *J.*, 1922, 121, 2381; C. K. Ingold and C. W. Shoppee, *J.*, 1929, 447.

dienone is also formed.⁵⁴ In the colchicine field, attempted cyclisation of the acid (LII) fails through displacement of bromine and the formation of a bromo-derivative of the indanone (LIII).^{55, 56} A possible synthesis, involving ring-expansion of the Buchner type applied to the central ring of phenanthrene, appears to be blocked by unusual stability in the dibenznorcadienecarboxylic acid (XIV) produced from the adduct of the hydrocarbon and ethyl diazoacetate.^{46, 57} On the other hand, an improved method for converting ethylenic compounds into *cis*-diols is now available in the use of osmium tetroxide in presence of pyridine, with benzene as solvent or diluent.⁵⁸ Thereby the diol is precipitated as a coloured crystalline complex of the osmic ester with pyridine, and is liberated when the complex, dissolved in methylene chloride, is shaken with an aqueous-alkaline solution of mannitol. The process has been applied with success to hydroxylation of the 9 : 10-double bond of phenanthrene, and diols are likewise obtained⁵⁹ from a number of polycyclic aromatic hydrocarbons including chrysene, pyrene, 1 : 2-benzanthracene, 1 : 2 : 5 : 6-dibenzanthracene, 3 : 4-benzpyrene, and 20-methylholanthrene. It is also applicable to 9-methylphenanthrene⁶⁰ from which the diol (LV) is formed and is cleaved by lead tetra-acetate, the resulting keto-aldehyde (LVI) undergoing cyclisation to the known trienone (I). By similar means 2 : 3 : 4 : 7-tetramethoxy-10-methylphenanthrene is converted into the trienone (LVII) which is identical with the unsaturated ketone, obtained as part-product from the oxidation of deaminocolchinel methyl ether with dichromate (p. 193). It may be hoped that future developments along these or related lines will provide decisive evidence for the structure of colchinel methyl ether.

J. D. L.

6. RECENT WORK ON THE REACTIONS OF ORGANIC SULPHUR COMPOUNDS.

This report discusses some of the more important synthetical uses of organic sulphur compounds. A comprehensive account of the hydrogenolysis of these compounds by means of Raney nickel is included. Some of the reactions, for example the Willgerodt-Kindler reaction, have no counterpart in the oxygen series, whilst in others the use of sulphur compounds rather than their oxygen analogues takes advantage of their greater reactivity.

Hydrogenolysis.—The removal of sulphur or its replacement by hydrogen by means of Raney nickel was first discovered by J. Bougault, E. Cattelain,

⁵⁴ J. v. Braun and G. Manz, *Annalen*, 1929, **468**, 258; compare G. T. Dickson, Ph.D. Thesis, Glasgow, 1948.

⁵⁵ H. R. Frank, P. E. Fanta, and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1948, **70**, 2314.

⁵⁶ N. Barton, J. W. Cook, and J. D. Loudon, *in the press*.

⁵⁷ N. L. Drake and T. R. Sweeney, *J. Org. Chem.*, 1946, **11**, 67.

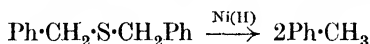
⁵⁸ R. Criegee, B. Marchand, and H. Wannowius, *Annalen*, 1942, **550**, 99.

⁵⁹ J. W. Cook and R. Schoental, *J.*, 1948, 170.

⁶⁰ G. L. Buchanan, J. W. Cook, J. D. Loudon, and J. MacMillan, *Nature*, 1948, **162**, 692.

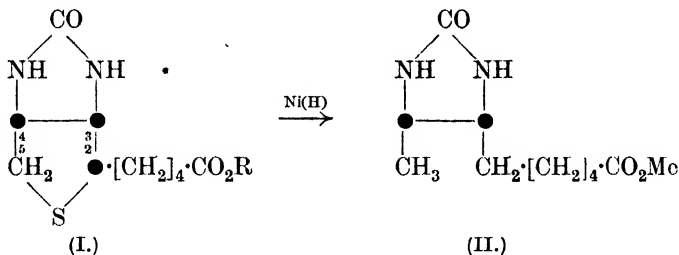
and P. Chabrier.^{1, 2} It has since been employed widely for the preparation and study of the structures of organic compounds.

The reaction is carried out with Raney nickel prepared in the usual way,³ or by employing the modification of R. Mozingo and his collaborators.⁴ Recently H. Adkins and H. R. Billica⁵ have described the preparation of a more active catalyst which they designate "W-6." Such catalysts, represented by Ni(H) in this report, retain hydrogen which brings about the hydrogenolysis. For example, when benzyl sulphide in ethanol was heated under reflux for two hours with Raney nickel in the absence of a hydrogen atmosphere, toluene was obtained in 85% yield.⁴ The mechanism of this reaction has not been established, but it has been suggested⁶ that it involves



attack by atomic hydrogen with intermediate formation of free radicals since, for example, R. Mozingo, C. Spencer, and K. Folkers⁷ record the formation of *N*-ethylaniline in 43% yield by hydrogenolysis of hydrazo-benzene in ethanol.

Under similar conditions benzoyl-L(-)-cystine, prepared from natural cystine, afforded benzoyl-L(+)-alanine, *i.e.*, racemisation did not occur.⁴ That natural methionine has the same absolute configuration as the other L- α -amino-acids was demonstrated in the same way. The benzoyl derivative of synthetic D(+)-methionine yielded D(-)- α -aminobutyric acid,⁸ which has been correlated with D(-)-alanine, while the same derivative of natural (-)-methionine gave L(+)- α -aminobutyric acid.¹⁰ In connection with studies on the structure of β -biotin (I; R = H), the methyl ester



(I; R = Me) was desulphurised to dethiobiotin methyl ester (II).¹¹ β -Biotin contains three asymmetric carbon atoms (●), and hence four racemic forms

¹ *Ann. Reports*, 1945, **42**, 100.

² *Compt. rend.*, 1939, **208**, 657.

³ *Org. Synth.*, 1941, **21**, 15.

⁴ R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013.

⁵ *Ibid.*, 1948, **70**, 695.

⁶ G. W. Kenner, B. Lythgoe, and A. R. Todd, *J.*, 1948, 957.

⁷ *J. Amer. Chem. Soc.*, 1944, **66**, 1859.

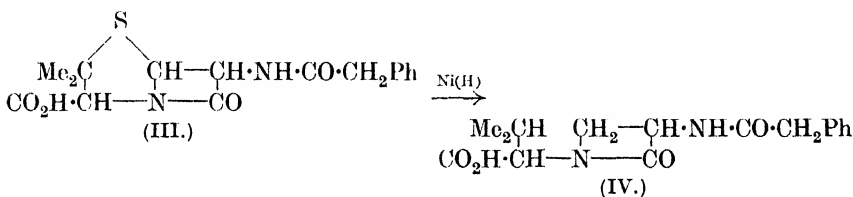
⁸ G. S. Fonken and R. Mozingo, *ibid.*, 1947, **69**, 1212.

⁹ G. W. Clough, *J.*, 1918, 526.

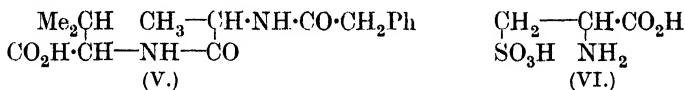
¹⁰ K. Vogler, *Helv. Chim. Acta*, 1947, **30**, 1766.

¹¹ V. du Vigneaud, B. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy, and S. A. Harris, *J. Biol. Chem.*, 1942, **146**, 475.

should be capable of existence. Three of these have been synthesised by R. Mzingo, K. Folkers, and their co-workers¹² and one by A. Grussner, J.-P. Bourquin, and O. Schnider.¹³ The stereochemical relationship of these racemates was deduced by studying their hydrogenolysis and hydrolysis.¹³ Two of the racemates yielded the same DL-dethiobiotin, and therefore differ only in the configuration at C₂, whereas the third racemate must have a different arrangement of its nitrogen atoms at C₃ and C₄. The study of dethiobenzylpenicillin by the Merck chemists was of great importance in the elucidation of the structure and stereochemistry of benzylpenicillin.^{14, 15} When an aqueous solution of sodium benzylpenicillin (III) was heated for



a short time with Raney nickel, three products were formed. One of these, dethiobenzylpenicillin, was shown to possess the structure (IV), and provided strong evidence for the β -lactam formulation of penicillin. Another of the products was identified as *N*-phenylacetyl-L-(+)-alanyl-D(-)-valine



(V). Although it was considered unlikely that intramolecular rearrangement had occurred during the formation of dethiobenzylpenicillin, this possibility has been made less likely by the work of H. Adkips, F. J. Brutschy, and M. McWhirter.¹⁶ Using the very active W-6 Raney nickel catalyst,⁵ these workers were able to remove sulphur from sodium benzylpenicillin in 96% alcohol under about 45 lb./sq. in. of hydrogen in a period of four hours at 10–20°, and obtained a fair yield of dethiobenzylpenicillin identical with that of R. Mzingo, K. Folkers *et al.* A summary of the desulphurisation studies on benzylpenicillin and related compounds is given by A. H. Cook¹⁵ and need not be discussed further.

Sulphur in higher states of oxidation than that in thiols and sulphides can also be displaced by Raney nickel. For example, diphenyl sulfoxide (Ph·SO·Ph) and diphenyl sulphone (Ph·SO₂·Ph) gave 75% and 65% yields respectively of benzene. However, toluene-*p*-sulphonic acid and its methyl ester, and cysteic acid (VI) are unaffected¹⁷ (cf. the reductive displacement

¹² *Ann. Reports*, 1944, **41**, 217.

¹³ *Ibid.*, 1946, **43**, 240.

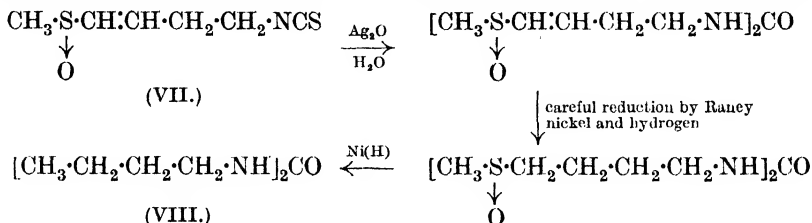
¹⁴ "The Chemistry of Penicillin," edited by H. T. Clarke, J. R. Johnson, and (Sir) R. Robinson, Oxford University Press, 1949.

¹⁵ A. H. Cook, *Quarterly Reviews*, 1948, **2**, 203–259.

¹⁶ *J. Amer. Chem. Soc.*, 1948, **70**, 2610.

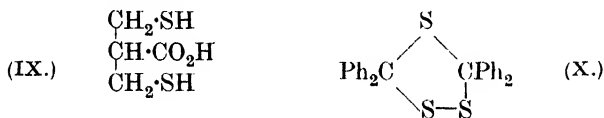
¹⁷ Merck and Co. Inc., PEN X46 (Report to the Therapeutic Research Corporation of Great Britain). Cf. ref. 120.

of the sulphonic acid group from *o*- and *m*-sulphobenzoic acids by means of nickel-aluminium alloy in the presence of alkali¹⁸). Another example of the hydrogenolysis of a sulfoxide is provided by the work of H. Schmid and P. Karrer¹⁹ on the constitution of sulphoraphen (VII) from radish seed (*Raphanus sativus* L. var. alba). By the following series of reactions sulphoraphen was converted into *NN'*-di-*n*-butylurea (VIII). It is interesting to note that sulphoraphen, which is optically active, is the first known naturally



occurring substance of which the optical activity does not depend upon the presence of an asymmetric carbon atom.

A sulphur-containing compound isolated from asparagus has been examined by E. F. Jansen²⁰ and shown to be $\beta\beta'$ -dimercaptoisobutyric acid (IX). On hydrogenolysis it was converted into isobutyric acid. The structure of the trisulphide produced from thiobenzophenone and dry



air has been shown to be (X).²¹ Oxidation by means of chlorine in the presence of water gave *ca.* two molecules of benzophenone dichloride, while treatment with Raney nickel gave *ca.* two molecules of diphenylmethane. In the same way difluorenyl trisulphide was shown to possess an analogous structure. In their investigations on the reactions of sulphur with monoolefins and $\Delta^{1:5}$ -diolefins, E. H. Farmer and F. W. Shipley²² showed that the products obtained were monomeric and not cross-linked by carbon-carbon bonds. This was shown by submitting them to the hydrogenolysis reaction.

The hydrogenolysis of mercaptals ($>\text{C}(\text{SR})_2 \rightarrow >\text{CH}_2$) provides a useful alternative to the well-known Wolff-Kishner²³ and Clemmensen²⁴ reductions. This method has been used by H. Hauptmann in the steroid series,²⁵ and has been developed by M. L. Wolfrom and J. V. Karabinos as a general method.²⁶ H. Hauptmann found that ethylenedithiol readily condensed

¹⁸ E. Schwenk, D. Papa, B. Whitman, and H. Ginsberg, *J. Org. Chem.*, 1944, **9**, 1.

¹⁹ *Helv. Chim. Acta*, 1948, **31**, 1017.

²⁰ *J. Biol. Chem.*, 1948, **176**, 657.

²¹ E. Campaigne and W. B. Reid, *J. Org. Chem.*, 1947, **12**, 807.

²² *J.*, 1947, 1519.

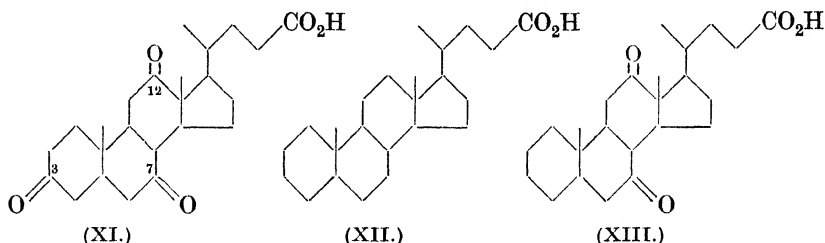
²³ "Organic Reactions" (R. Adams), 1948, Vol. IV.

²⁴ *Ibid.*, 1942, Vol. I.

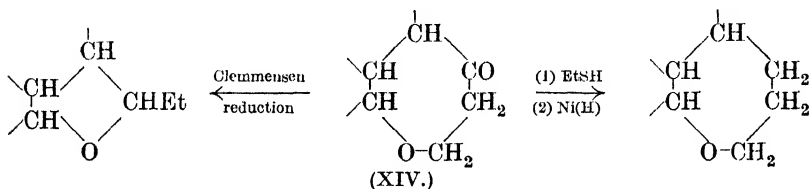
²⁵ *Anais Assoc. Quim. Brasil*, 1944, **3**, 231; *J. Amer. Chem. Soc.*, 1947, **69**, 562.

²⁶ *Ibid.*, 1944, **66**, 909.

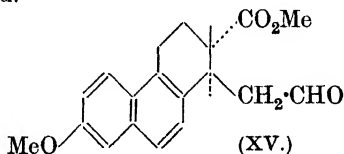
with all three keto-groups of 3:7:12-triketocholanic acid (XI), whereas monothiols reacted only at C₃. Thus, (XI) can be converted either into cholanic acid (XII) or into 7:12-diketocholanic acid (XIII). Many other



similar transformations have been carried out in the steroid series.^{25, 27, 28} The fact that this reaction occurs under milder conditions than in the Wolff-Kishner and Clemmensen reactions has been utilised by R. B. Wood-



ward and W. J. Brehm²⁹ to reduce the carbonyl group of methoxymethylchanodihydrostrychnone (XIV, part formula) without causing structural rearrangement. J. Heer and K. Miescher showed that no rearrangement occurred during the Wolff-Kishner reduction of (XV) [an intermediate in their conversion of (+)-equilenin methyl ether into (+)- β -bisdehydrodoisynolic acid],³⁰ by converting the aldehyde into the dibenzylmercaptal and heating it with aqueous ethanolic Raney nickel, exactly the same product being obtained.³¹



Other applications of this type of reduction of carbonyl groups include studies on the structure of streptomycin³² and the synthesis of 1- and 2-deoxy-sugar alcohols.²⁶ For example, D-galactose diethylmercaptal penta-

²⁷ S. Bernstein and L. Dorfmann, *J. Amer. Chem. Soc.*, 1946, **68**, 1152.

²⁸ L. Norymberska, J. Norymberski, and A. Olalde, *ibid.*, 1948, **70**, 1256.

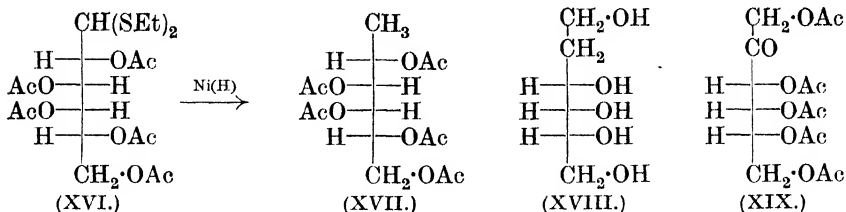
²⁹ *Ibid.*, 1948, **70**, 2107.

³⁰ *Ann. Reports*, 1947, **44**, 196.

³¹ *Helv. Chim. Acta*, 1948, **31**, 405.

³² F. A. Kuehl, junr., E. H. Flynn, N. G. Brink, and K. Folkers, *J. Amer. Chem. Soc.*, 1946, **68**, 2096; 1948, **70**, 2085; I. R. Hooper, L. H. Klemm, W. J. Polglase, and M. L. Wolfrom, *ibid.*, 1946, **68**, 2120; 1947, **69**, 1052; R. V. Lemieux, W. J. Polglase, C. W. de Walt, and M. L. Wolfrom, *ibid.*, 1946, **68**, 2747.

acetate (XVI) gave 1-deoxy-D-galactitol penta-acetate (XVII) in 66% yield. An attempt to prepare 2-deoxy-D-allitol (XVIII) from D-psicose penta-

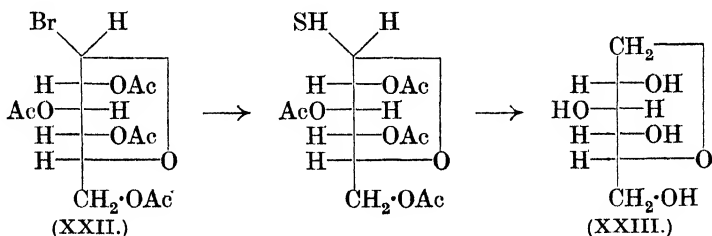


acetate (XIX) by this method was unsuccessful.³³ The product actually obtained, after hydrolysis, was *mesohexane-1 : 3 : 4 : 6-tetraol* (XX). During attempted formation of the diethylmercaptal of (XIX), an acetate group



on C₅ had evidently been replaced by the ethylthio-group, giving (XXI) which yielded the tetra-acetate of (XX) on hydrogenolysis.

The removal of sulphur from the requisite intermediates has been used for the preparation of 1 : 5-anhydrides of sugar-alcohols.³⁴ The method, which appears to be quite general, may be illustrated by the synthesis of a 1 : 5-D-sorbitan (polygalitol) (XXIII) from acetobromo-D-glucose (XXII) in 1943.³⁴ The action of sodium thiomethoxide on 2 : 3-anhydro-sugar derivatives gives either the 2- or the 3-methylthio-sugar derivative depending



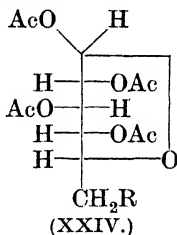
on the stereochemistry of the particular sugar. Hydrogenolysis of these sulphur-containing intermediates has been used by D. A. Prins, T. Reichstein, and their co-workers³⁵ for the synthesis of deoxyhexoses and by S. Mukerjee and A. R. Todd³⁶ for a deoxypentose. An example of this

³³ M. L. Wolfrom, B. W. Lew, and R. M. Goepp, junr., *J. Amer. Chem. Soc.*, 1946, **68**, 1443.

³⁴ C. S. Hudson and H. G. Fletcher, junr., *ibid.*, 1943, **65**, 1477; 1947, **69**, 706, 921, 1672; 1948, **70**, 310.

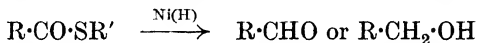
³⁵ *Helv. Chim. Acta*, 1946, **29**, 371, 1061; 1947, **30**, 496, 743. ³⁶ *J.*, 1947, 969.

type of synthesis has been given in a previous report.³⁷ Another type of reaction in the sugar series has been described by E. Hardegger and R. M. Montavon.³⁸ In the synthesis of 1:2:3:4-tetra-acetyl 6-deoxy-D-glucose (quinovose tetra-acetate) (XXIV; R = H) from D-glucose, the



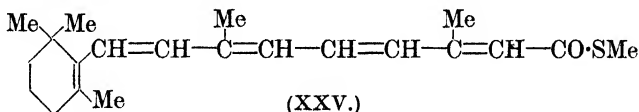
authors encountered unexpected difficulty in the reductive displacement of iodine from the iodide (XXIV; R = I). The difficulty was surmounted by converting the iodide into the thiouronium salt [XXIV; R = S·C(NH)·NH₂·HI], followed by treatment with Raney nickel; the product (XXIV; R = H) was then obtained in 70% yield (based on the iodide).

Hydrogenolysis of thioesters has been reported to yield aldehydes³⁹ or alcohols.⁴⁰ The use of freshly-prepared Raney nickel apparently leads



to the formation of alcohols, but by first deactivating the catalyst (by heating under reflux in acetone under standard conditions) aldehydes can be prepared in good yield.⁴¹ The preparation of aldehydes by this method has been applied to simple aromatic and aliphatic compounds,³⁹ steroids,^{41, 42} and to the conversion of tetra-acetyl-D-ribonic acid into *aldehydo*-D-ribose tetra-acetate.³⁹ Thioesters are easily obtained by the action of acid chlorides on thiols in pyridine. This route to aldehydes is a good alternative to the Rosenmund reduction of acid chlorides.²³

An interesting application of the method has been mentioned by J. F. Arens and D. A. van Dorp.⁴³ Reformatsky reaction²⁴ of methyl bromothiolacetate (Br·CH₂·CO·SMe) with the C₁₈-ketone related to vitamin A gave an oily product probably containing the methylthioester (XXV) of



vitamin A acid. The Dutch workers are studying the action of Raney nickel on this and other αβ-unsaturated thioesters.

³⁷ *Ann. Reports*, 1946, **43**, 176.

³⁸ *Helv. Chim. Acta*, 1946, **29**, 1129.

³⁹ M. L. Wolfrom and J. V. Karabinos, *J. Amer. Chem. Soc.*, 1946, **68**, 724, 1455.

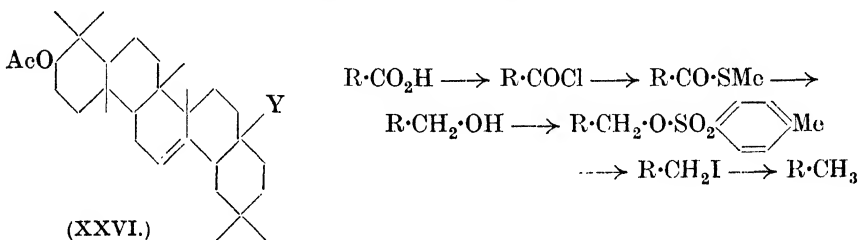
⁴⁰ V. Prelog, J. Norymberski, and O. Jeger, *Helv. Chim. Acta*, 1946, **29**, 360.

⁴¹ G. B. Spero, A. V. McIntosh, junr., and R. H. Levin, *J. Amer. Chem. Soc.*, 1948, **70**, 1907.

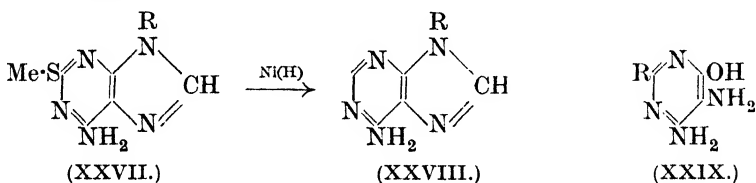
⁴² A. V. McIntosh, junr., E. M. Meinzer, and R. H. Levin, *ibid.*, 1948, **70**, 2955.

⁴³ *Rec. Trav. chim.*, 1947, **66**, 407.

The conversion of acids into alcohols *via* the thiolesters has been employed extensively. It is found that aliphatic, aromatic, and heterocyclic acids can be smoothly converted into the corresponding alcohols, usually in 60—90% yield.^{40–42, 44, 45} This application has been of special use in the triterpene field,^{40, 44, 46} where progress in the determination of structure depends largely upon relating new compounds with known ones by means of simple reactions. In this connection the partial or complete reduction of carboxyl groups plays an important part. The usual alternative methods of reduction generally involve strongly acid or alkaline conditions, whereas the hydrogenolysis of thiolesters can be carried out in neutral solution. There is no risk of saturation of double bonds or of the hydrolysis of acyl protective groups (except the formyl group⁴²); for example, acetyloleanolic acid (XXVI; Y = CO₂H) has been converted into β-amyrin acetate (XXVI; Y = Me) by the following sequence⁴⁰ (R·CO₂H = acetyloleanolic acid).



Several 9-alkyl- and 9-glycosido-adenines (XXVIII) have been synthesised by B. Lythgoe, A. R. Todd, and their co-workers⁴⁷ by a general method involving the hydrogenolysis of 2-methylthio-9-substituted adenines (XXVII) as the last stage:



Adenine itself (XXVIII; R = H) has been thus obtained from 2-mercaptoadenine.⁴⁸ The useful intermediate, 5:6-diamino-4-hydroxypyrimidine (XXIX; R = H), has been prepared similarly from the corresponding 2-mercapto-compound (XXIX; R = SH).⁴⁹ In the latter case the more

⁴⁴ O. Jeger, J. Norymberski, S. Szpilfogel, and V. Prelog, *Helv. Chim. Acta*, 1946, **29**, 684.

⁴⁵ J. Heer and K. Miescher, *ibid.*, 1947, **30**, 777; E. Sorkin, W. Krähenbuhl, and H. Erlenmeyer, *ibid.*, 1948, **31**, 65; B. Prijs, A. H. Lutz, and H. Erlenmeyer, *ibid.*, p. 571.

⁴⁶ O. Jeger, C. Nisoli, and L. Ruzicka, *ibid.*, 1946, **29**, 1183; O. Jeger and W. Hofer, *ibid.*, 1948, **31**, 157; L. Ruzicka, S. Szpilfogel, and O. Jeger, *ibid.*, 1946, **29**, 1520.

⁴⁷ *J.*, 1945, 556; 1947, 355; 1948, 965.

⁴⁸ A. F. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3109.

⁴⁹ R. O. Roblin, junr., J. O. Lampen, J. P. English, Q. F. Cole, and J. R. Vaughan, *junr.*, *ibid.*, 1945, **67**, 290.

usual method for the replacement of the mercapto-group by hydrogen in heterocyclic rings (namely by oxidation with nitric acid or hydrogen peroxide⁵⁰) led to the anomalous formation of the 2-hydroxy-derivative (XXIX; R = OH).

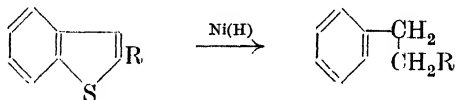
In a series of papers on the azoles, A. H. Cook, (Sir) I. M. Heilbron, and their co-workers⁵¹ have made considerable use of hydrogenolysis to ascertain the structures of various intermediates. They find that 2-mercapto- and 2:4(5)-dimercapto-glyoxalines are readily desulphurised.



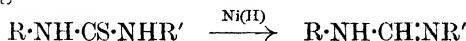
The sulphur atom in the thiazole ring system is unaffected by mild treatment with Raney nickel; thus, a number of 2-mercaptothiazoles have yielded thiazoles. On the other hand, thiophen and methylthiophen are



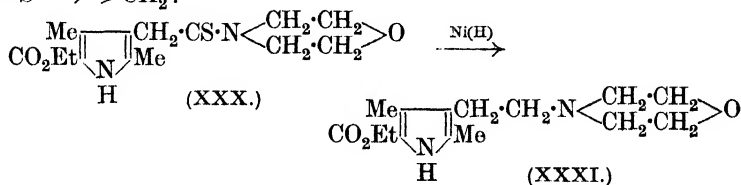
apparently disrupted,¹ while thianaphthens are converted into phenyl-substituted ethanes.⁵² Disubstituted formamidines can be obtained from



the corresponding thioureas:⁵³



In contrast to the behaviour of the thione group ($>\text{C}=\text{S}$) in thioureas and heterocyclic systems, where it appears to exist in the thiol ($\geq\text{C}-\text{SH}$) form, the thio-amide (XXX) yielded the amine (XXXI) involving the change $>\text{C}=\text{S} \longrightarrow >\text{CH}_2$:⁵⁴



The latter reaction is similar to the electrolytic reduction of open-chain⁵⁵

⁵⁰ J. Houben, "Die Methoden der organischen Chemie," 3rd Edn., 1925, Vol. II, p. 197.

⁵¹ J., 1947, 1598; 1948, 201, 1262, 1337, 1340.

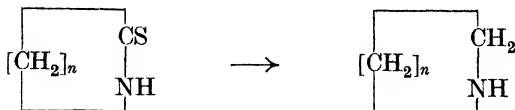
⁵² F. F. Blicke and D. G. Sheets, *J. Amer. Chem. Soc.*, 1948, **70**, 3768.

⁵³ R. de B. Ashworth, *J.*, 1948, 1716.

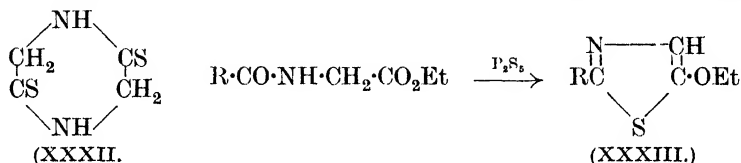
⁵⁴ D. L. Turner, *J. Amer. Chem. Soc.*, 1948, **70**, 3961.

⁵⁵ K. Kindler and W. Peschke, *Arch. Pharm.*, 1932, **270**, 340.

and cyclic ⁵⁶ thio-amides to amines, although under certain conditions aldimines are produced.^{55a}

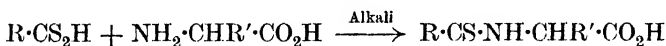


Thioacylation.—Thio-amides can be prepared by the action of phosphorus pentasulphide on the corresponding amide,⁵⁷ but this method sometimes fails,⁵⁸ especially when applied to peptides.⁵⁹ E. S. Gatewood and T. B. Johnson ⁶⁰ prepared ethyl thiobenzamidoacetate ($\text{Ph}\cdot\text{CS}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$) and 2 : 5-dithionpiperazine (XXXII) by this method, and other American workers ⁶¹ have reported the preparation of methyl phenylthioacetamido-



acetate ($\text{Ph}\cdot\text{CH}_2\cdot\text{CS}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2\text{Me}$) by the combined action of phosphorus pentasulphide and potassium sulphide on the corresponding ester. Under more drastic conditions the action of this reagent on acylamido-esters leads to 5-alkoxythiazoles ^{62, 63} (XXXIII).

A very mild method of preparing thioformamides has been developed by A. R. Todd, B. Lythgoe, and their co-workers,^{58, 64} namely, the action of potassium dithioformate on the amine at room temperature. This important method has been extended to the use of dithiophenylacetic acid ^{65, 66} and dithiohexoic acid ^{67, 68} for the preparation of thioacylamido-acids.



^{55a} K. Kindler, *Annalen*, 1923, **431**, 193.

⁵⁶ L. Ruzicka, M. W. Goldberg, M. Hürbin, and H. A. Boekennoogen, *Helv. Chim. Acta*, 1933, **16**, 1323.

⁵⁷ A. W. Hofmann, *Ber.*, 1878, **11**, 338; A. Bernthsen, *ibid.*, 1878, **11**, 503.

⁵⁸ A. R. Todd, F. Bergel, Karimullah, and R. Keller, *J.*, 1936, 1557; 1937, 361.

⁵⁹ M. Backes, *Compt. rend.*, 1947, **225**, 533. ⁶⁰ *J. Amer. Chem. Soc.*, 1926, **48**, 2900.

⁶¹ Heyden Chemical Corporation, CPS 574 (Report to the Committee for Penicillin Synthesis of the Medical Research Council).

⁶² E. Miyamichi, *J. Pharm. Soc. Japan*, 1926, **528**, 103.

⁶³ Imperial Chemical Industries, Ltd., CPS 634, 693.

⁶⁴ A. R. Todd, *Pedler Lecture, J.*, 1946, 647; *Ann. Reports*, 1944, **41**, 200.

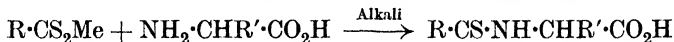
⁶⁵ (a) E. P. Abraham, W. Baker, E. Chain, and (Sir) R. Robinson, CPS 43; (b) *idem*, CPS 71; (c) *idem*, CPS 74; (d) *idem*, CPS 438.

⁶⁶ A. H. Cook, J. A. Elvidge, and (Sir) I. M. Heilbron, CPS 199; Upjohn Co., CPS 265, 292; Squibb Institute for Medical Research, CPS 277, 278, 330; Lilly Research Laboratories, CPS 286, 317; Merck and Co., Inc., CPS 289, 307.

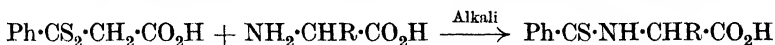
⁶⁷ Private communication from J. B. Jepson and (Sir) R. Robinson; J. B. Jepson, D.Phil. Thesis, Oxford, 1946.

⁶⁸ C. I. Brodrick, D. A. Peak, F. F. Whitmont, and W. Wilson, CPS 592.

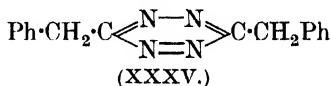
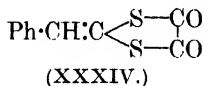
Dithio-acids are unstable and decompose on keeping. Dithioformic⁵⁸ and dithiophenylacetic⁶⁹ acids are best stored as the stable potassium salts. Dithio-esters are stable, and the methyl esters of dithiophenylacetic^{68, 70} and dithio-*n*-hexoic⁷¹ acids have been used for thioacylation. Dithiobenzoic acid is less reactive than the aliphatic dithio-acids and does not



react with glycine or leucine even on warming.⁷² Amino-acids can, however, be thiobenzoylated by means of carboxymethyl dithiobenzoate.⁷³



Unfortunately aliphatic dithio-acids (except dithioformic⁷⁴ and dithiophenylacetic⁷⁵) cannot be obtained in good yield. However, aliphatic⁶⁹ and aromatic^{67, 76} thion-esters ($R \cdot CS \cdot OR'$) can be used in place of dithio-esters, and they are easily prepared by the action of hydrogen sulphide on iminoethers.⁷⁷ Thiobenzoyl chloride⁷⁸ ($Ph \cdot CSCO$), prepared by the action of oxalyl chloride or thionyl chloride on dithiobenzoic acid, is reported to react vigorously with aniline to give thiobenzanilide,⁷⁸ but does not react in the expected way with amino-acids.⁷⁹ Attempts to prepare thiophenylacetyl chloride ($Ph \cdot CH_2 \cdot CSCO$) were unsuccessful; oxalyl chloride and potassium dithiophenylacetate yielded⁶⁹ 4 : 5-diketo-2-benzylidene-1 : 3-dithiolan (XXXIV). Attempts to prepare the potentially-useful thiophenyl-



acetyl azide ($Ph \cdot CH_2 \cdot CS \cdot N_3$) were also unsuccessful, since the dithio-acid did not react with sodium azide, while methyl dithiophenylacetate and hydrazine gave 3 : 6-dibenzyl-1 : 2 : 4 : 5-tetrazine (XXXV) and other products instead of the desired hydrazide.⁸⁰ Thiobenzhydrazide has been

⁶⁹ W. Baker and J. F. W. McOmie, unpublished results; J. F. W. McOmie, D.Phil. Thesis, Oxford, 1946.

⁷⁰ A. R. Todd and A. Topham, CPS 93; J. Wardleworth, A. R. Todd, P. Sykes, J. Baddiley, and H. T. Openshaw, CPS 351; R. Bentley, J. R. Catch, A. H. Cook, (Sir) I. M. Heilbron, and G. Shaw, CPS 267, 328; E. P. Abraham, W. Baker, E. Chain, and (Sir) R. Robinson, CPS 342; Lilly Research Laboratories, CPS 286, 364; W. E. Bachmann, CPS 335, 358; Squibb Institute for Medical Research, CPS 452.

⁷¹ A. H. Cook, J. A. Elvidge, and (Sir) I. M. Heilbron, CPS 273.

⁷² Squibb Institute for Medical Research, CPS 278.

⁷³ B. Holmberg, "The Svedberg Memorial Volume," p. 299, Stockholm, 1944; *Arkiv Kemi Min. Geol.*, 1944, 17 A, 1; D. F. Elliot, *Nature*, 1948, 162, 658.

⁷⁴ T. G. Levi, *Gazzetta*, 1924, 54, 395.

⁷⁵ J. Houben, *Ber.*, 1906, 39, 3227.

⁷⁶ (a) E. P. Abraham, E. Chain, W. Baker, and (Sir) R. Robinson, B.P. 588,101, 1947; (b) A. A. Goldberg and W. Kelly, *J.*, 1948, 1919.

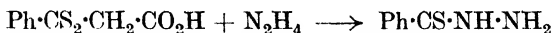
⁷⁷ Y. Sakurada, *Mem. Coll. Sci. Kyoto*, 1926, 9, 237.

⁷⁸ H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, 1920, 3, 824.

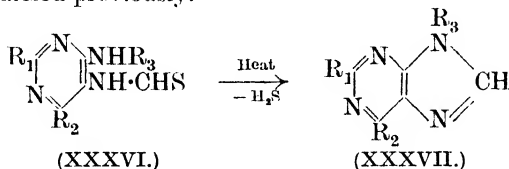
⁷⁹ Squibb Institute for Medical Research, CPS 301.

⁸⁰ A. H. Cook, J. A. Elvidge, and (Sir) I. M. Heilbron, CPS 328.

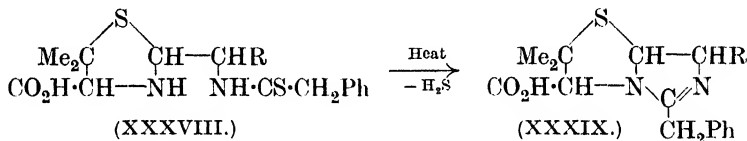
prepared by B. Holmberg,⁷³ but its reaction with nitrous acid has not been tried.⁸¹



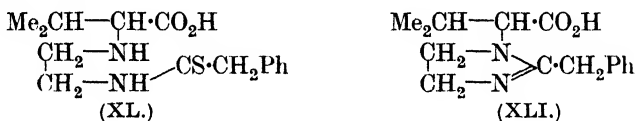
Synthesis of Heterocyclic Compounds.—The extensive work of B. Lythgoe, A. R. Todd, and their co-workers on the ring closure of 5-thioformamido-pyrimidines of type (XXXVI) to the purine nucleoside derivatives (XXXVII) has been summarised previously.⁶¹



Benzylpenillamine (XXXIX; R = H) has been synthesised by heating the thiazolidine (XXXVIII) in quinoline.^{65b, 82} The yield obtained in this



way was much better than by the dehydration of the corresponding acylamidomethylthiazolidine.⁸³ Attempts to convert the thiazolidine (XXXVIII; R = CO₂Et) into monoethyl penillate (XXXIX; R = CO₂Et) were unsuccessful.⁸⁴ The compound (XL), unlike its oxygen analogue, readily cyclised on heating to give the dihydroglyoxaline (XLI).⁸⁵



Thioacylamido-acids on cyclisation yielded derivatives of thiazole or oxazole depending upon the reagents employed. Phosphorus tribromide gave the thiazolones (XLII; R = Ph and CH₂Ph).⁶⁷ Similarly 2-benzyl-4-*p*-methoxybenzylthiazol-5-one was obtained from the corresponding thioacylamido-acid by the action of acetic anhydride.⁸⁶ The latter reagent in the presence of pyridine gave 5-acetoxy-thiazoles (XLIII; R = Ph and CH₂Ph).⁶⁷ Benzaldehyde and acetic anhydride gave the 4-benzylidene-thiazolone (XLVI; R = CH₂Ph),^{65c} while ethyl orthoformate and acetic anhydride yielded the compound (XLV; R = CH₂Ph).^{65c, 87} On the

⁸¹ Private communication from B. Holmberg, 1948.

⁸² A. H. Cook, J. A. Elvidge, and (Sir) I. M. Heilbron, CPS 77.

⁸³ *Idem*, CPS 67.

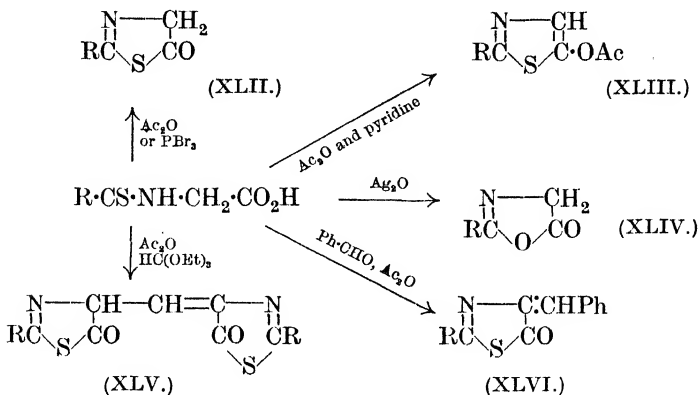
⁸⁴ W. E. Bachmann, CPS 358.

⁸⁵ Upjohn Co., CPS 258, 292.

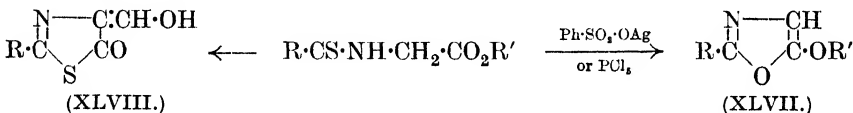
⁸⁶ Merck and Co., Inc., CPS 307.

⁸⁷ The same compound was obtained, but assigned a different structure, by V. du Vigneaud, CPS 470.

other hand, the oxazole derivatives (XLIV; R = Ph and CH₂Ph) were obtained by the action of silver oxide in the cold.^{65a, 67, 76a}

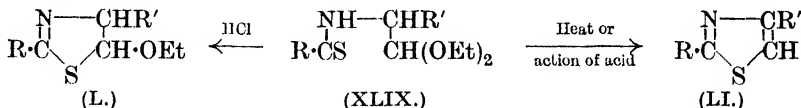


Thioacylamido-esters can also be cyclised to give derivatives of thiazole or oxazole. Thus, the 5-alkoxy-oxazoles (XLVII; R = Ph or CH₂Ph,



R' = Et and XLVII; R = Ph, R' = Me) can be prepared from the appropriate esters by the action of silver benzenesulphonate^{88, 68} and phosphorus pentachloride⁶⁷ respectively. The formylation of methyl or ethyl phenylthioacetamidoacetate by formic ester in the presence of sodium ethoxide caused simultaneous ring closure to give 2-benzyl-4-hydroxy-methylenethiazol-5-one (XLVIII; R = CH₂Ph).^{72, 79}

Phenylthioacetamidoacetaldehyde diethyl acetal (XLIX; R = CH₂Ph, R' = H) on warming with alcoholic hydrogen chloride gave 5-ethoxy-2-benzylthiazoline (L; R = CH₂Ph, R' = H),^{65a} whilst the action of methyl



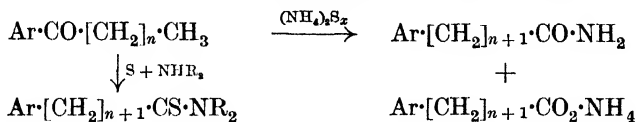
n-dithiohexoate on aminoacetal gave the thiazoline (L; R = *n*-C₅H₁₁, R' = H) directly.⁷¹ The action of acid or heat on the compound (XLIX; R = CH₂Ph, R' = CO₂H) gave, however, the thiazolecarboxylic acid (LI; R = CH₂Ph, R' = CO₂H).^{68, 89}

The Willgerodt-Kindler Reaction.—The conversion of aryl alkyl ketones into ω -aryl aliphatic acid derivatives by the action of an aqueous solution of ammonium polysulphide at high temperatures was first described by

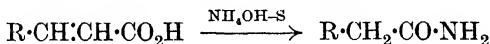
⁸⁸ C. I. Brodrick, D. A. Peak, and F. F. Whitmont, CPS 446.

⁸⁹ Lilly Research Laboratories, CPS 317.

C. Willgerodt.⁹⁰ The use of an anhydrous amine and sulphur, in place of the polysulphide, was studied by K. Kindler.⁹¹ In this case a thio-amide is

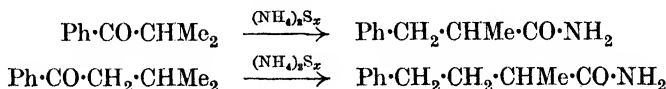


formed which can be hydrolysed to the carboxylic acid or reduced to the primary amine.⁹¹ These reactions and subsequent improvements in the experimental procedure have been reviewed by M. Carmack and M. A. Spielman,⁹² but several important papers have appeared since then.⁹³⁻¹⁰⁹ It is clear that the modified Willgerodt-Kindler reaction is one of the best methods for the preparation of a wide variety of aliphatic, aromatic, and heterocyclic substituted acetic acids from the corresponding methyl ketones. The yields become progressively less as n , in the scheme above, is increased. The original reaction has been extended to include, as starting materials, secondary^{93, 94} and tertiary alcohols,^{95, 101} primary, secondary, and tertiary thiols,^{94, 95} disulphides,⁹⁸ aldehydes,⁹² trithioacetophenone,¹⁰³ imines,⁹² phenyldimorpholinomethane,⁹⁸ olefins, and acetylenes.⁹² $\alpha\beta$ -Unsaturated acids gave derivatives of the next lower acid.¹⁰² Benzylamine heated with morpholine and sulphur gave thiobenzmorpholide⁹⁹ and under the same



conditions α -tetralone gave 4- β -naphthylmorpholine.¹⁰⁴ J. Stanek¹⁰⁵ has found that derivatives of acids are formed by heating the following with sulphur: ketoximes, acetophenone-azine, -hydrazone, and -phenylhydrazon.

The mechanism of this reaction has been studied by several groups of workers. J. A. King and F. H. McMillan⁹⁴ were the first to bring forward definite evidence that no rearrangement of the carbon skeleton occurred. They showed that when the reaction was carried out on *isobutyrophenone* and *isovalerophenone*, the products were the amides of the α -methyl- β -



phenylpropionic and - γ -phenylbutyric acids respectively. They also found that the reaction did not take place if the alkyl chain contained a quaternary

⁹⁰ *Ber.*, 1887, **20**, 2467.

⁹¹ *Annalen*, 1923, **431**, 196, 225.

⁹² "Organic Reactions," (R. Adams), 1946, Vol. III, 83-107.

⁹³ J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.*, 1946, **68**, 525.

⁹⁴ *Idem, ibid.*, 1946, **68**, 632. ⁹⁵ *Idem, ibid.*, p. 1369. ⁹⁶ *Idem, ibid.*, p. 2335.

⁹⁷ *Idem, ibid.*, 1947, **69**, 1207.

⁹⁸ *Idem, ibid.*, 1948, **70**, 4143.

⁹⁹ F. H. McMillan, *ibid.*, 1948, **70**, 868.

¹⁰⁰ M. Carmack and DeLos F. DeTar, *ibid.*, 1946, **68**, 2025, 2029, 2755.

¹⁰¹ D. B. Pattison and M. Carmack, *ibid.*, pp. 2033, 2755.

¹⁰² C. H. Davis and M. Carmack, *J. Org. Chem.*, 1947, **12**, 76.

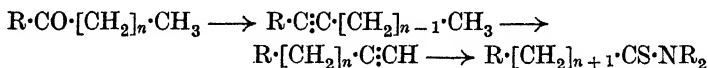
¹⁰³ E. Campaigne and P. V. Rutan, *J. Amer. Chem. Soc.*, 1947, **69**, 1211.

¹⁰⁴ W. J. Horton and J. Van den Berghe, *ibid.*, 1948, **70**, 2425.

¹⁰⁵ *Coll. Czech. Chem. Comm.*, 1947, **12**, 691.

carbon atom; thus the only product obtained from pivalophenone was neopentylbenzene formed by reduction. In the same year E. M. Shantz and D. Rittenberg,¹⁰⁶ using acetophenone containing excess of ¹³C in the carbonyl group, also proved the retention of the carbon skeleton during the reaction. Simultaneously M. Calvin and his co-workers¹⁰⁷ carried out similar experiments using ¹⁴C in the carbonyl group of acetophenone. They concluded, however, that "the amide formed in the Willgerodt reaction . . . does not involve a migration of carbon atoms. The phenylacetic acid, however, appears to be formed by a different mechanism involving migration of a carbon atom." The complete details of the experimental work which gave this remarkable result have not yet been published. If it is rigorously established that some migration does occur, then at least two mechanisms must co-exist under the same reaction conditions.

Theories concerning the mechanism of the reaction have been put forward by K. Kindler,¹⁰⁸ M. Carmack and DeLos F. DeTar,^{92, 100} and J. A. King and F. H. McMillan.^{94, 98} The first postulates the migration of an aryl group to the end of the chain, two or more carbon atoms removed from the original carbonyl group, and this theory is therefore improbable. The other workers consider that the fundamental mechanism of the reaction, as applied to aldehydes, ketones, olefins, etc., is the same, whether it is carried out under the conditions used by C. Willgerodt or by K. Kindler. M. Carmack and DeLos F. DeTar postulated a series of steps involving the elimination of the elements of water to give an acetylene, migration of the triple bond to the end of the chain, followed by reaction with sulphur and the amine to give a thio-amide. In the presence of hot aqueous ammonia thio-amides are unstable,¹¹⁰ and hence are not normally isolated in the



Willgerodt reaction. The carboxyamides formed by hydrolysis of the thio-amides are, however, relatively very stable under the same reaction conditions. Slow hydrolysis to the ammonium salts accounts for the presence of small amounts of the latter in the reaction product. This mechanism is clearly inapplicable to branched-chain compounds and the authors admit that there may be at least two different mechanisms, one of which can operate effectively only in unbranched alkyl chains.

J. A. King and F. H. McMillan have put forward a detailed reaction

¹⁰⁶ *J. Amer. Chem. Soc.*, 1946, **68**, 2109.

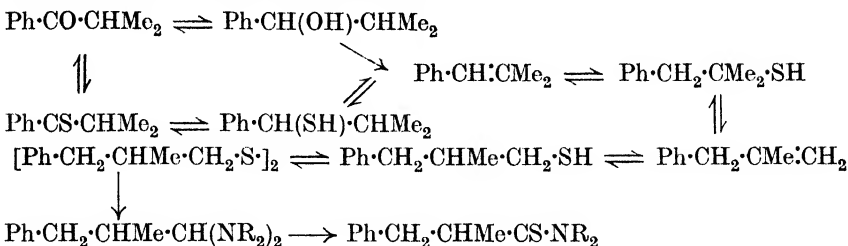
¹⁰⁷ W. G. Dauben, J. C. Reid, P. E. Yankwich, and M. Calvin, *ibid.*, 1946, **68**, 2117.

¹⁰⁸ K. Kindler and T. Li, *Ber.*, 1941, **74**, 321.

¹⁰⁹ E. Schwenk and D. Papa, *J. Org. Chem.*, 1946, **11**, 798; H. Gilman and S. Avakian, *J. Amer. Chem. Soc.*, 1946, **68**, 2104; A. C. Ott, L. A. Mattano, and G. H. Coleman, *ibid.*, p. 2633; R. L. Malan and P. M. Dean, *ibid.*, 1947, **69**, 1797; D. L. Turner, *ibid.*, 1948, **70**, 396; J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead, and O. K. Behrens, *ibid.*, pp. 2837, 2843.

¹¹⁰ A. Bernthsen, *Annalen*, 1877, **184**, 297.

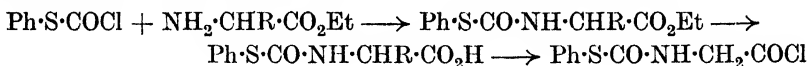
mechanism which is supported by a wealth of experimental evidence. The proposed sequence is as follows (for *isobutyrophenone*) :



The authors point out⁹⁸ the interesting fact that the Willgerodt–Kindler reaction is the only known one in which a primary thiol undergoes ultimate oxidation to a carboxylic acid derivative, *i.e.*, oxidation of the carbon instead of only the sulphur atom. This unique conversion is discussed from a theoretical standpoint in the same paper.

The relation between the Willgerodt-Kindler reaction and the formation of dithio-acids from aldehydes by the action of hydrogen persulphide in the presence of a condensing agent (such as zinc chloride),¹¹¹ or ammonium polysulphide under mild conditions, is not at all clear. If dithio-acids occur as intermediates in the Willgerodt-Kindler reaction (cf. ref. 94) then the use of a tertiary amine might be expected to lead to the formation of a substituted ammonium salt of a dithio-acid. Attempts to confirm this have not been successful.¹¹³

Protective Groups.—A new method for the protection of amino-groups has been outlined by G. C. H. Ehrensvärd.¹¹⁴ α -Amino-esters can be acylated with *S*-phenyl chlorothiolformate. The acylated esters can be hydrolysed by acid [to which the protective group (Ph·S·CO·) is very stable]



and converted into the acid chlorides for peptide syntheses. Removal of the protective group is accomplished by heating with lead acetate solution in 70% ethanol or in the cold by N/10-alkali in the presence of lead hydroxide or carbonate.

Aldehyde groups can be protected by conversion into mercaptals, and can be regenerated by treatment of the latter with mercuric chloride in the presence of cadmium carbonate. This is useful for the preparation of the acyl derivatives of the free *aldehyde*- or *keto*-forms of the sugars.¹¹⁵ Recent

¹¹¹ I. Bloch, F. Hohn, and G. Bugge, *J. pr. Chem.*, 1910, **82**, 473; D.R.-P. 214,888, 1908.

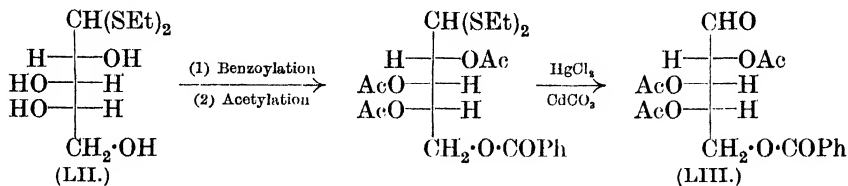
¹¹² G. N. White, *Proc.*, 1914, 37; G. Bruni and T. G. Levi, *Gazzetta*, 1924, 54, 389.

¹¹³ Private communication from J. A. King.

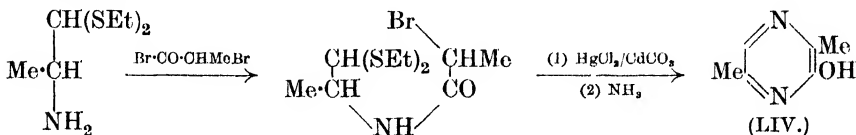
¹¹⁴ *Nature*, 1947, 159, 500.

¹¹⁵ P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, 1926, **69**, 175; 1927, **74**, 695; M. L. Wolfson, *J. Amer. Chem. Soc.*, 1929, **51**, 2188; F. Micheel and F. Suckfüll, *Annalen*, 1933, **502**, 85.

examples of the method include the synthesis of 5-benzoyl-2 : 3 : 4-triacetyl-L-arabinose (LIII) from L-arabinose diethyl mercaptal ¹¹⁶ (LII), and of



2-hydroxy-3 : 6-dimethylpyrazine (LIV) from α -aminopropaldehyde diethyl mercaptal. ¹¹⁷



The protection of amino-groups by conversion into their toluene-*p*-sulphonamides, and later removal of the group by reductive fission with sodium in liquid ammonia is of considerable use in the peptide field, since optically active amino-acids are not racemised by this treatment. ^{118, 119} Attempts to remove the protective group from toluene-*p*-sulphonylglycine and *N*-benzyglycine by hydrogenolysis with Raney nickel were unsuccessful. ¹²⁰

Miscellaneous Reactions.—Toluene-*p*-sulphonyl and methanesulphonyl chlorides find use in the preparation of anhydro-sugars ¹²¹ and in the replacement of the hydroxyl group by hydrogen by the reaction sequence ($\text{R}' = \text{Me}$ or *p*-Me-C₆H₄): ¹²²



The synthesis of aromatic aldehydes by the method of J. S. McFadyen and T. S. Stevens ¹²³ has been extended to thiazole-, ¹²⁴ pyrimidine-, ¹²⁵ pyridine-, ¹²⁶ and quinoline-aldehydes. ¹²⁷ It has also been applied to the synthesis of thyronine [4-(4'-hydroxyphenoxy)phenylalanine]. ¹²⁸ The

¹¹⁶ G. W. Kenner, B. Lythgoe, and A. R. Todd, *J.*, 1948, 960.

¹¹⁷ R. A. Baxter, G. T. Newbold, and F. S. Spring, *J.*, 1947, 370.

¹¹⁸ V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, 1937, **117**, 27.

¹¹⁹ D. W. Wooley, *ibid.*, 1948, **172**, 71.

¹²⁰ Unpublished observations by W. D. Ollis and J. F. W. McOmie; cf. ref. 17.

¹²¹ *Ann. Reports*, 1939, **36**, 258.

¹²² *E.g.*, F. Reber and T. Reichstein, *Helv. Chim. Acta*, 1946, **29**, 343, and K. Folkers *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2325.

¹²³ *J.*, 1936, 584.

¹²⁴ E. R. Buchmann and E. M. Richardson, *J. Amer. Chem. Soc.*, 1939, **61**, 891.

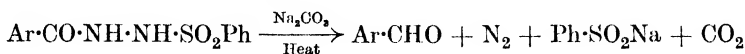
¹²⁵ D. Price, E. L. May, and F. D. Pickel, *ibid.*, 1940, **62**, 2818.

¹²⁶ L. Panizzon, *Helv. Chim. Acta*, 1941, **24**, 24.

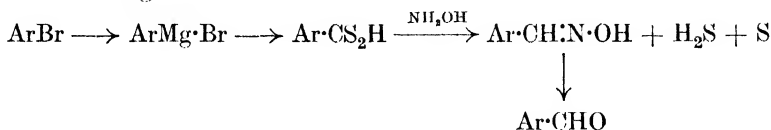
¹²⁷ A. H. Cook, I. M. Heilbron, and L. Steger, *J.*, 1943, 413.

¹²⁸ C. R. Harington and R. V. P. Rivers, *J.*, 1940, 1101.

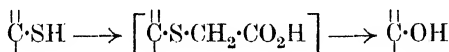
method, however, fails completely where the initial carboxyl group is not attached directly to the ring system.^{123, 125} Aromatic aldehydes can also



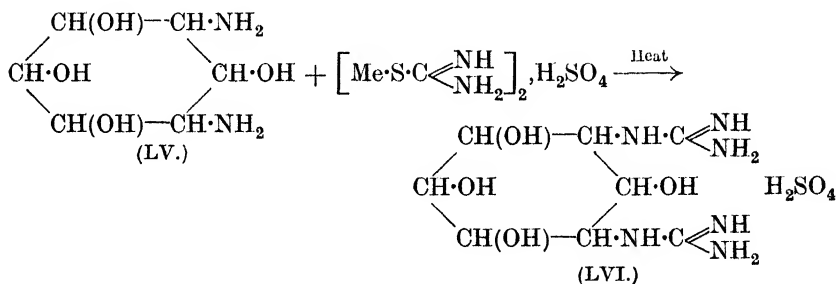
be prepared by the action of dithio-acids on *as*-phenylmethylhydrazine,¹²⁹ semicarbazide,¹³⁰ or hydroxylamine.¹³¹ The reaction sequence is typical for all three reagents :



Thiourea is often used in the synthesis of pyrimidines and purines,¹³² from which the sulphur atom can be removed by hydrogenolysis or by oxidation (see earlier), or replaced by oxygen by hydrolysis in the presence of chloroacetic acid.^{133, 134} *S*-Methylthiuronium sulphate reacts with amines



on heating to give substituted guanidines. Streptidine (LVI) has been synthesised from streptamine (LV) using this reaction.¹³⁵ It has also been used for the synthesis of guanidines and diguanidines for therapeutic trial.¹³⁶



Rhodanine¹³⁷ can be used for the preparation of α -amino-acids and for

¹²⁹ H. Wuyts and M. Goldstein, *Bull. Soc. chim. Belg.*, 1931, **40**, 497.

¹³⁰ H. Wuyts, L. Berman, and A. Lacourt, *ibid.*, 1931, **40**, 665; L. I. Smith and J. Nichols, *J. Org. Chem.*, 1941, **6**, 489.

¹³¹ H. Wuyts and H. Koeck, *Bull. Soc. chim. Belg.*, 1932, **41**, 196.

¹³² W. Traube, *Annalen*, 1903, **331**, 64.

¹³³ T. B. Johnson, G. M. Pfau, and W. W. Hodge, *J. Amer. Chem. Soc.*, 1912, **34**, 1041.

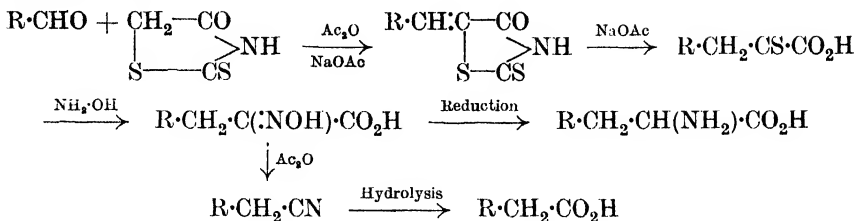
¹³⁴ M. Polonovski and D. Libermann, *Bull. Soc. chim.*, 1947, **14**, 1073; J. Elks, B. A. Hems, and B. E. Ryman, *J.*, 1948, 1386.

¹³⁵ M. L. Wolfrom and W. J. Polglase, *J. Amer. Chem. Soc.*, 1948, **70**, 1672.

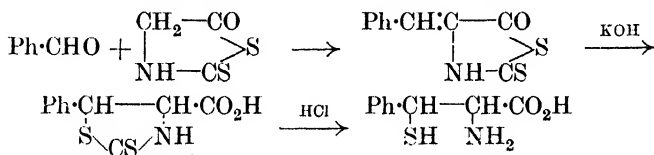
¹³⁶ *E.g.*, F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray, and F. L. Rose, *J.*, 1948, 1630.

¹³⁷ C. Gräner, *Helv. Chim. Acta*, 1922, **5**, 610; 1923, **6**, 458.

the conversion of substituted benzaldehydes into the corresponding aryl-acetic acids.^{137, 138}



α -Amino- β -mercapto-acids, *e.g.*, β -phenylcysteine,¹³⁹ are now readily accessible, starting from 2-thiothiazolidone, itself prepared from aminomethyl cyanide and carbon disulphide.¹⁴⁰ The same intermediate can also be



used for the synthesis of α -amino-acids, since it has been shown that hydro-genolysis of β -phenylcysteine with Raney nickel gives phenylalanine.¹³⁹

J. F. W. McO.

7. HETEROCYCLIC COMPOUNDS.

Aziridines.

The polymerisation of ethyleneimine and its homologues and the industrial utilisation of the products (*e.g.*, as paper strengtheners,¹ stabilisers for halogeno-compounds,² adhesives,³ anti-corrosion agents,⁴ for vulcanisation accelerators,⁵ in base exchange resins,⁶ in connection with the dyeing of synthetic films and fibres,⁷ and as plastics⁸) have received attention since about 1936. Only more recently has any noticeable interest been taken in the possible usefulness of ethyleneimines in chemical synthesis.

H. Wenker's method⁹ for making ethyleneimine, which involves conversion of ethanolamine into aminoethylsulphuric acid (procedure recently modified¹⁰ to give 95% yields), followed by cyclisation with alkali, has

¹³⁸ P. L. Julian and B. M. Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126; N. Campbell and J. E. McKail, *J.*, 1948, 1251.

¹³⁹ R. Chatterjee, A. H. Cook, (Sir) I. M. Heilbron, and A. L. Levy, *J.*, 1948, 1337.

¹⁴⁰ A. H. Cook, (Sir) I. M. Heilbron, and A. L. Levy, *J.*, 1948, 201.

¹ G. M. Kline, *Modern Plastics*, 1945, **23**, No. 2, 152A.

² D.R.-P. 732,087; 742,427.

³ Belg.P. 446,422.

⁴ U.S.P. 2,304,623.

⁵ U.S.P. 2,376,796.

⁶ W. Lautsch, *Die Chemie*, 1944, **57**, 149.

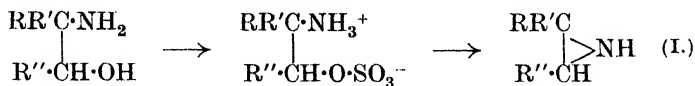
⁷ T. S. Gardner, *J. Polymer Sci.*, 1946, **1**, 289; D.R.-P. 714,790.

⁸ U.S.P. 2,382,185; 2,381,020; D.R.-P. 724,037; 738,667.

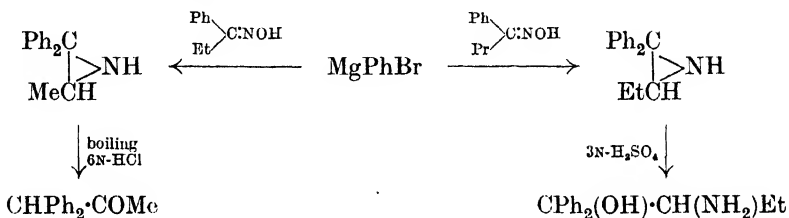
⁹ *J. Amer. Chem. Soc.*, 1935, **57**, 2328.

¹⁰ P. A. Leighton, W. A. Perkins, and M. L. Renquist, *ibid.*, 1947, **69**, 1540.

been extended. T. L. Cairns¹¹ prepared 2:2-dimethylethyleneimine (I; R = R' = Me; R'' = H) starting from 2-amino-2-methylpropan-1-ol,

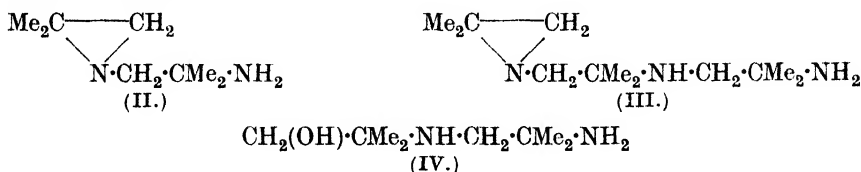


and G. D. Jones¹² has obtained the homologues (I; R = Me and Et, R' = R'' = H; R = R'' = Me, R' = H; R = R' = Me, R'' = Me and Pr) mostly in 45–65% yields. The method appears much superior to the cyclisation of halogeno-amines, though it is not applicable to the preparation of 2:2:3:3-tetra-substituted aziridines. A novel route to tri-substituted ethyleneimines, developed by K. N. Campbell and his co-workers,¹³ involves the interaction of ketoximes with excess of aryl Grignard reagents in concentrated solution:



The hydrolyses shown served to establish the ethyleneimine structures.

In a study of the polymerisation of ethyleneimines by hydrogen chloride (probably a bimolecular reaction), G. D. Jones and his co-workers¹⁴ concluded that polyethyleneimine is a linear poly-secondary amine of chain length of 25–100 units. W. Kern and E. Brenneisen¹⁵ had earlier found that, under the influence of hydrogen bromide or boron trifluoride, ethyleneimine formed straight- and branched-chain polymers but that 70% of the product was only dimeric. 2:2-Dimethylethyleneimine when polymerised by dilute hydrochloric acid¹² affords a water-insoluble basic wax together with a low molecular-weight fraction shown to consist largely of the compounds (II), (III), and (IV).



The conversion of ethyleneimines into substituted ethylenediamines has been achieved by reaction with primary or secondary amines in the

¹¹ *J. Amer. Chem. Soc.*, 1941, **63**, 871.

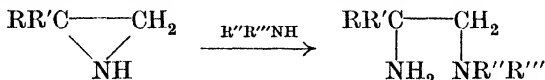
¹² *J. Org. Chem.*, 1944, **9**, 484.

¹³ K. N. Campbell, B. K. Campbell, J. F. McKenna, and E. P. Chaput, *ibid.*, 1943, **8**, 103.

¹⁴ G. D. Jones, A. Langsjoen, M. M. C. Neumann, and J. Zomlefer, *ibid.*, 1944, **9**, 125.

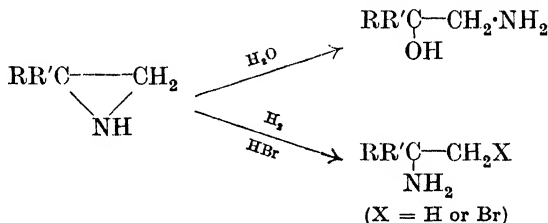
¹⁵ *J. pr. Chem.*, 1941, **159**, 193.

presence of water,¹⁶ aluminium chloride,¹⁷ or aqueous mineral acid,¹⁸ but none of the methods is suitable for preparing the anhydrous diamines. L. B. Clapp¹⁹ finds that the reaction proceeds well under anhydrous conditions at 100° with ammonium chloride as catalyst. In this manner 2-ethylethyleneimine with liquid ammonia (40-fold excess) gives 1:2-butylenediamine, in 55% yield, and very little polymer, while with various alkyl- and *cyclo*alkyl-amines (in 3-fold excess) 2-amino-1-alkylamino-*n*-butanes ($R = Et$, $R' = H$) are formed. 2-Amino-1-alkylaminoisobutanes ($R = R' = Me$) arise from 2:2-dimethylethyleneimine:

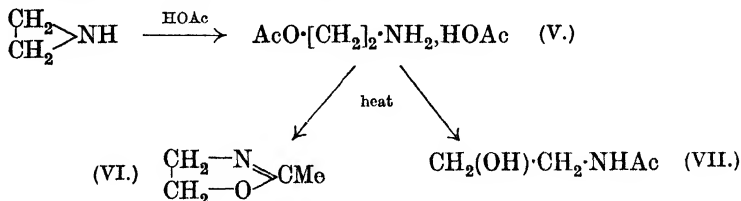


Ring opening therefore occurs preferentially at the primary carbon. However, in the case of reactions with aniline appreciable amounts (9–22%) of the alternative ring-scission products are also formed.

Only a few examples of the above type of reaction (substituted-aziridine ring-scission) have previously been recorded. Catalytic hydrogenation²⁰ and reaction with hydrogen bromide²¹ proceed with ring opening at the primary carbon, whereas hydrolysis¹⁰ occurs with scission at the tertiary carbon rather than at the primary (or secondary,¹³ see above):



When a mixture of ethyleneimine and acetic acid at -78° warms to room temperature 2-acetoxyethylammonium acetate (V) is formed,²² which



¹⁶ U.S.P. 2,318,729.

¹⁷ A. L. Coleman and J. E. Callen, *J. Amer. Chem. Soc.*, 1946, **68**, 2006.

¹⁸ G. I. Braz and V. A. Skorodumov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1947, **55**, 315.

¹⁹ *J. Amer. Chem. Soc.*, 1948, **70**, 184.

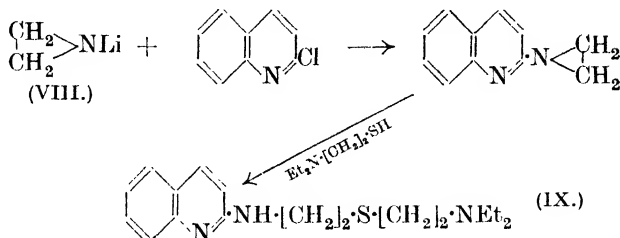
²⁰ J. V. Karabinos and K. T. Serijan, *ibid.*, 1945, **67**, 1856; K. N. Campbell, A. H. Sommers, and B. K. Campbell, *ibid.*, 1946, **68**, 140.

²¹ S. Gabriel and H. Ohle, *Ber.*, 1917, **50**, 804.

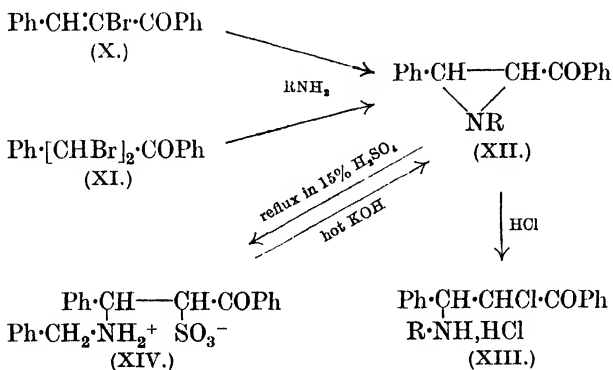
²² G. D. Jones, J. Zomlefer, and K. Hawkins, *J. Org. Chem.*, 1944, **9**, 500.

on heating in an open vessel^{cf. 23} loses acetic acid and water and cyclises to 2-methyl- Δ^2 -oxazoline (VI); in a closed system re-arrangement to 2-acet-amido ethanol (VII) occurs.

An example of possible further applications of ethyleneimines in synthetic work is the preparation by H. Gilman *et al.*²⁴ of ethyleneiminyl-lithium (VIII) which was employed for the synthesis of a quinoline derivative (IX) as follows :



A new class of aziridine derivatives has been discovered by N. H. Cromwell and his co-workers²⁵ who observed that interaction of phenyl α -bromostyryl ketone (X) and phenyl 1:2-dibromo-2-phenylethyl ketone (XI) with benzylamine and *cyclohexylamine* afforded colourless products. From ultra-violet absorption data²⁶ and chemical evidence these products were concluded²⁷ to be ethyleneimine ketones and not compounds of the type $\text{Ph} \cdot \text{CO} \cdot \text{CH} : \text{CPh} \cdot \text{NHR}$ as had earlier been suggested :^{28, cf. 29}



Treatment²⁵ of the products (XII) with hydrogen chloride resulted in the uptake of two molecules of the acid and formation of chloro-amine salts

²³ H. Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079.

²⁴ H. Gilman, N. N. Crounse, S. P. Massie, junr., R. A. Benkeser, and S. M. Spatz, *ibid.*, 1945, **67**, 2106.

²⁵ N. H. Cromwell, R. D. Babson, and C. E. Harris, *ibid.*, 1943, **65**, 312.

²⁶ N. H. Cromwell and R. S. Johnson, *ibid.*, p. 316.

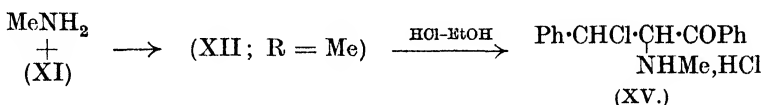
²⁷ N. H. Cromwell and J. A. Caughlan, *ibid.*, 1945, **67**, 2235.

²⁸ S. Ruhemann and E. R. Watson, *J.*, 1904, 1181.

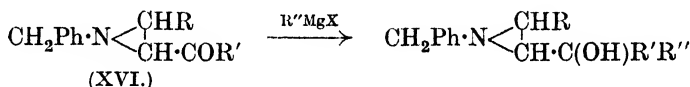
²⁹ J. Agar, A. Hickey, and P. G. Sherry, *Proc. Roy. Irish Acad.*, 1943, **49**, B, 109.

(XIII). In dry ether, the hydrochloride of (XII; R = CH₂Ph) could also be obtained. With sulphuric acid, (XII; R = CH₂Ph) yielded a high-melting, sparingly soluble substance which, in view of its ready reversion into (XII; R = CH₂Ph) by treatment with alkali, was formulated as the internal salt (XIV).

Methylamine was also found²⁷ to condense with (XI) to form an imine (XII; R = Me), the aziridine structure of which was well substantiated by its reaction with hydrogen chloride to yield (XV), ring opening having occurred in opposite sense to that previously observed :



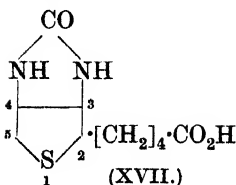
Additional evidence in support of the aziridine structures of these imino-ketones has recently been obtained.³⁰ Thus the products (XVI; R = Ph, R' = *p*-Me·C₆H₄) and (XVI; R = *p*-Me·C₆H₄, R' = Ph), derived from benzylamine and the appropriate αβ-dibromo-ketones in ethanol at >40°, were found to react merely as normal ketones with Grignard reagents, affording the corresponding carbinols :



Possible open-chain structures are consequently ruled out, and incidentally the behaviour indicates that the ethyleneimine ring is stabilised by the introduction of an alkyl substituent in the 1-position.

β-Biotin.

Stereochemical Studies.—In the previous Report on biotin³¹ evidence concerning the configurations of the four racemates of (XVII), (±)-, (±)-*epi*-, (±)-*epiallo*-, and (±)-*allo*-biotin, was reviewed. This evidence suggested that the configurations about the C₃-C₄ linkage were *trans* in (±)-*allo*- and (±)-*epiallo*biotin, whereas in (±)-biotin the C₃-C₄ configuration was *cis*. More recently these conclusions have been rigidly verified by B. R. Baker and his associates. These workers have elaborated methods of obtaining singly any of the four racemates of (XVII), starting from only one intermediate (XXI; R = [CH₂]₄·CO₂H) : by chemical control of isomers the need to effect separations by fractional crystallisation was obviated. Besides providing new syntheses of (±)-biotin and (±)-

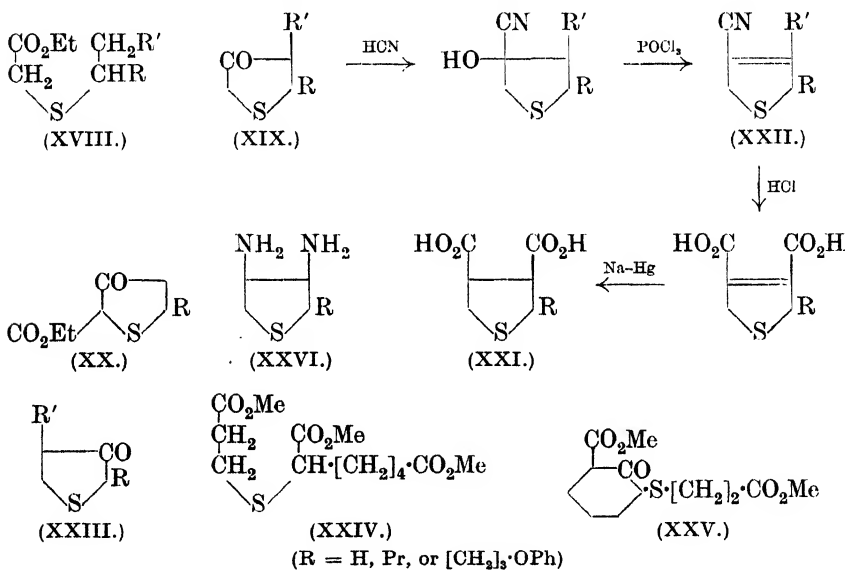


³⁰ N. H. Cromwell, *J. Amer. Chem. Soc.*, 1947, **69**, 258.

³¹ *Ann. Reports*, 1946, **43**, 239.

epiallobiotin the procedures have enabled the hitherto unknown (\pm)-*epibiotin* to be obtained. Though perfectly feasible, the synthesis of (\pm)-*allobiotin* from (XXI; $R = [CH_2]_4 \cdot CO_2H$) was not attempted. The work may conveniently be considered under two headings: (A) preparation of intermediates; (B) synthesis of biotin isomers.

(A) Dieckmann cyclisation of esters (XVIII; $R' = CO_2Et$ or CO_2Me) prepared from ethyl thioglycollate and $\alpha\beta$ -unsaturated esters gave mainly 4-ketothiophan-3-carboxylates (XIX; $R' = CO_2Et$ or CO_2Me) rather than the 5-isomers (XX).^{32, 33} This was shown by the fact that the derived acids (XIX; $R' = CO_2H$) were identical with corresponding acids obtained *via* the unambiguous cyclisation of the appropriate cyanides (XVIII; $R' = CN$) to (XIX; $R' = CN$). Preparation of the 2-substituted thiophan-3:4-dicarboxylic acids (XXI) was completed along conventional lines:



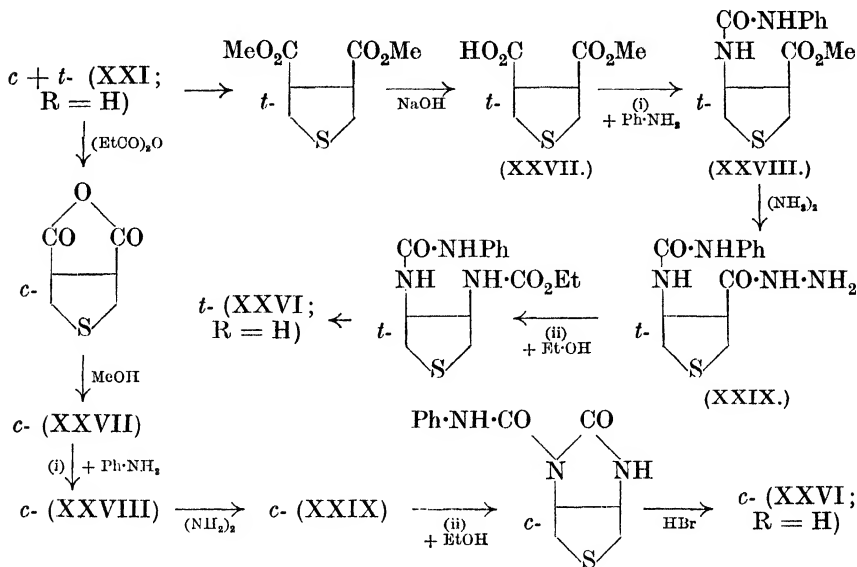
The double bond in (XXII) was shown to be in the 3:4-position by the observation that the same product could be derived from the structurally established intermediate (XXIII). The synthesis of (XXI; $R = [CH_2]_4 \cdot CO_2H$) by the above route proved highly unsatisfactory, however, since in this case (XX; $R = [CH_2]_4 \cdot CO_2Me$) (actually the 5-methyl ester) was the main product from the Dieckmann cyclisation.³⁴ Attempts to convert the compound (XXI; $R = [CH_2]_3 \cdot OPh$) *via* the bromide ($R =$

³² B. R. Baker, M. V. Querry, S. R. Safir, and S. Bernstein, *J. Org. Chem.*, 1947, **12**, 138.

³³ G. B. Brown, B. R. Baker, S. Bernstein, and S. R. Safir, *ibid.*, p. 155.

³⁴ G. B. Brown, M. D. Armstrong, A. W. Moyer, W. P. Anslow, junr., B. R. Baker, M. V. Querry, S. Bernstein, and S. R. Safir, *ibid.*, p. 160.

$[\text{CH}_2]_4\cdot\text{CO}_2\text{H}$) led to (\pm) -biotin and (\pm) -*epiallobiotin*.³⁸ The chemical and stereochemical configurations of the intermediates were checked at critical



$[t = trans, c = cis, (i) = \text{---} \rightarrow \text{COCl} \rightarrow \text{CON}_3 \rightarrow \text{NCO}, (ii) = \text{---} \rightarrow \text{CON}_3 \rightarrow \text{NCO}.]$

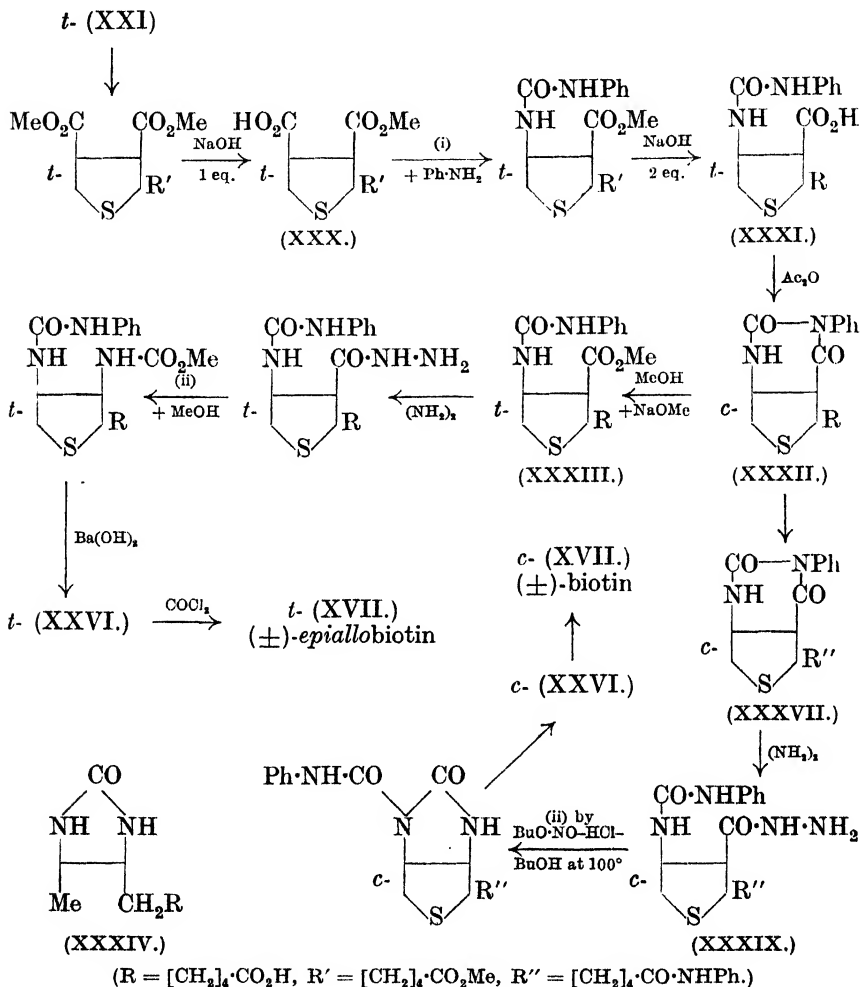
stages, *e.g.*, at (XXX), by chemical methods. It will be observed that inversion at C_3 was effected during stage (XXXI) \rightarrow (XXXII) and again during stage (XXXII) \rightarrow (XXXIII) so that the C_3 -acid, corresponding to the ester (XXXIII), was identical with (XXXI).

Of the known biotin racemates, (\pm) -*allo*- and (\pm) -*epiallo*-biotin both give microbiologically inactive dethiobiotin (XXXIV) and must consequently have the same configurations about C_3 - C_4 . (\pm) -Biotin gives rise to an active dethiobiotin and (\pm) -*epibiotin* would also afford the same isomer. The melting point of the *trans*-product *t*-(XVII) corresponded to that of the (\pm) -*epiallobiotin* of S. A. Harris *et al.*,³⁹ and was identified with certainty by Raney-nickel desulphurisation to a biologically inactive product: thus *t*-(XVII) could not have been the unknown (\pm) -*epibiotin*. A *trans*-configuration for the C_3 - C_4 link in (\pm) -*epiallo*- and (\pm) -*allo*biotin was thus rigidly established.³⁸ The *cis*-product *c*-(XVII) had 50% of the activity of natural biotin in assay against *L. arabinosus*, and resolution with L-arginine yielded (+)-biotin, identical with the natural vitamin. It followed that the remaining, unknown racemate, (\pm) -*epibiotin*, was also a *cis*-isomer, necessarily epimeric with (\pm) -biotin at C_2 .

³⁸ B. R. Baker, M. V. Querry, W. L. McEwen, S. Bernstein, S. R. Safir, L. Dorfman, and Y. Subbarow, *J. Org. Chem.*, 1947, **12**, 186.

³⁹ S. A. Harris, R. Mozingo, D. E. Wolf, A. N. Wilson, G. E. Arth, and K. Folkers, *J. Amer. Chem. Soc.*, 1944, **66**, 1800.

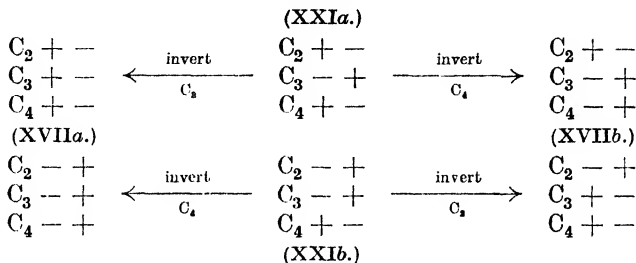
Because the synthetic methods enabled the configurations at C₃ and C₄ to be inverted selectively, a synthesis of (\pm)-*epi*biotin became possible.⁴⁰ It



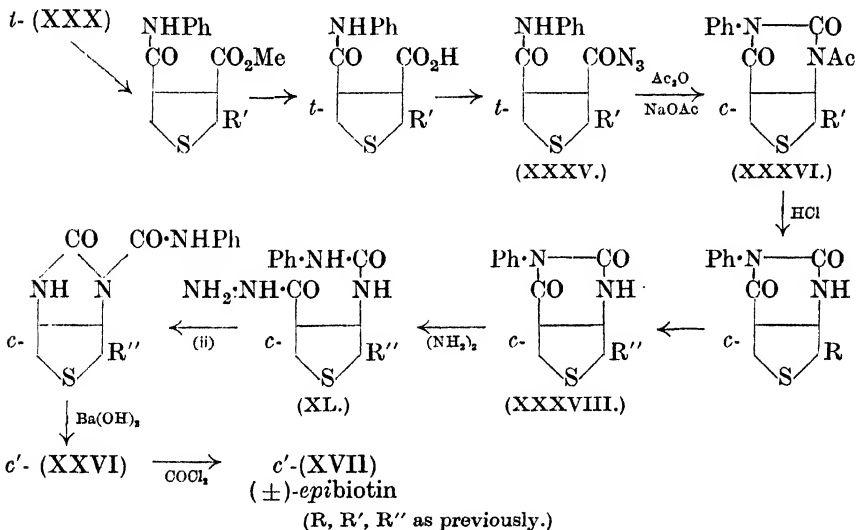
was apparent that the *trans*-racemate (XXI; R = [CH₂]₄·CO₂H) could have either of the total configurations (XXIa) or (XXIb). By inversion at C₃ and C₄ as indicated, both of the possible *cis*-C₃-C₄ racemates of biotin, (XVIIa) and (XVIIb), were obtainable irrespective of whether the actual configuration of the starting material was (XXIa) or (XXIb). Now in the previous reaction sequence a *cis*-configuration had been obtained by inversion at C₃ during the stage (XXXI) → (XXXII). If instead, a *cis*-

⁴⁰ B. R. Baker, W. L. McEwen, and W. N. Kinley, *J. Org. Chem.*, 1947, **12**, 322.

configuration were obtained by inversion at C_4 , at a suitable stage, the end product would, as already indicated, then be epimeric with the product



previously given, *i.e.*, it would be (\pm) -epibiotin. The correctness of this reasoning was demonstrated by the synthesis of (\pm) -epibiotin *c'*- (XVII) as follows, the structures of intermediates being proved where necessary :



It is to be noted that the reagents used for effecting the stage (XXXV) \rightarrow (XXXVI), *viz.* acetic anhydride-sodium acetate, caused inversion at C_4 but not at C_3 . Already established was the fact that in the Curtius rearrangement of an azide to an isocyanate no inversion occurred except when two adjacent carboxyls, attached to the thiophan (or penthian) nucleus, were degraded simultaneously. The need to convert the C_2 side chain carboxyl into anilide as at (XXXVII)³⁸ and (XXXVIII)⁴⁰ was occasioned by the fact that otherwise partial inversion took place at C_3 and C_4 , respectively, during the subsequent conversions into the acid hydrazides (XXXIX) and (XL). The primary effect of introducing the anilide group was to reduce very markedly the solubility of these compounds in the reaction medium.

To reiterate briefly, it is apparent that a configurational change can be effected selectively at nuclear substituents as follows: (a) at a carboxyl by boiling acetic or propionic anhydrides; (b) at an ester group by boiling alcohol containing a trace of sodium alkoxide; (c) at an anilide group by boiling acetic anhydride containing sodium acetate. Peculiar to the thiophan (and penthian) systems, and directionally uncontrollable, are (d) the inversion at one of two adjacent nuclear carboxyls during their simultaneous Curtius degradation *via* acid chlorides and sodium azide, and (e) the inversion at one of two adjacent ester groups during their conversion with hydrazine into acid hydrazides.

Pterins.

Since work in this field was previously reviewed⁴¹ progress has been made in several directions: new syntheses of vitamin B₆ (pteroylglutamic acid) and of pteric acid have been devised; the structure of the fermentation *Lactobacillus casei* factor has virtually been established; a new microbial growth factor, rhizopterin, has been isolated, identified, and synthesised; some experiments concerning reduction of the pteridine nucleus are reported; and a continued interest has been shown in the preparation of pteridine derivatives generally. Results previously announced in a preliminary manner, *e.g.*, the deduction of the structure and the synthesis of the liver *L. casei* factor (vitamin B₆) have now been established by the publication of full chemical details.^{42, 43, 44, 45, 46} Details of the method of isolation and purification of this factor have also been disclosed.⁴⁷ The precise nature of the anti-anæmia factor, "folic acid", originally obtained from vegetable sources by H. K. Mitchell and his co-workers⁴⁸ remains undetermined though evidence increasingly points to its being a mixture of closely related compounds with differing physiological activity.⁴⁹ On the other hand, a "norite eluate factor" isolated from liver and yeast in 1940,⁵⁰ is, according

⁴¹ *Ann. Reports*, 1946, **43**, 250.

⁴² E. L. R. Stokstad, B. L. Hutchings, J. H. Mowat, J. H. Boothe, C. W. Waller, R. B. Angier, J. Semb, and Y. SubbaRow, *J. Amer. Chem. Soc.*, 1948, **70**, 5.

⁴³ B. L. Hutchings, E. L. R. Stokstad, J. H. Mowat, J. H. Boothe, C. W. Waller, R. B. Angier, J. Semb, and Y. SubbaRow, *ibid.*, p. 10.

⁴⁴ J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. SubbaRow, *ibid.*, p. 14.

⁴⁵ C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. SubbaRow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, junr., *ibid.*, p. 19.

⁴⁶ M. E. Hultquist, E. Kuh, D. B. Cosulich, M. J. Fahrenbach, E. H. Northey, D. R. Seeger, J. P. Sickels, J. M. Smith, junr., R. B. Angier, J. H. Boothe, B. L. Hutchings, J. H. Mowat, J. Semb, E. L. R. Stokstad, Y. SubbaRow, and C. W. Waller, *ibid.*, p. 23.

⁴⁷ E. L. R. Stokstad, B. L. Hutchings, and Y. SubbaRow, *ibid.*, p. 3.

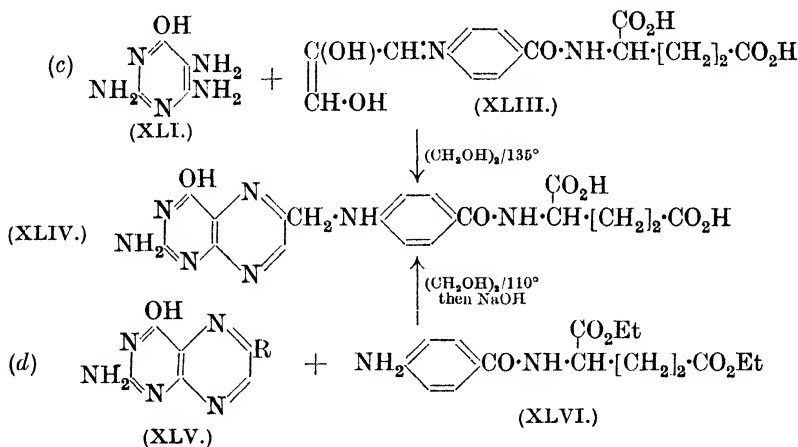
⁴⁸ H. K. Mitchell, E. E. Snell, and R. J. Williams, *ibid.*, 1941, **63**, 2284.

⁴⁹ D. A. Hall, *Biochem. J.*, 1947, **41**, 287, 294; cf. F. W. Chattaway, D. E. Dolby, and F. C. Happold, *ibid.*, 1948, **43**, 567.

⁵⁰ E. E. Snell and W. H. Peterson, *J. Bact.*, 1940, **39**, 273.

to E. L. R. Stokstad *et al.*,⁴² probably identical with vitamin B₆. Much of the current interest shown in the preparative field is fostered by the possibilities of synthesising alternative and more readily available anti-anæmia and growth factors, and of obtaining compounds which possess antagonistic actions. Compounds of the latter type might well prove to be of use⁵¹ for the chemotherapeutic treatment of conditions such as blood discrasias and leucæmia. A new aspect to the interest in pterins has been provided by the report⁵² that the fermentation *L. casei* factor causes regression of spontaneous breast tumours in mice.

Alternative Syntheses of Vitamin B₆ and Pteric Acid.—Preliminary communications, already outlined,⁴¹ have described the synthesis of vitamin B₆ from *p*-aminobenzoyl-L-glutamic acid, (a) by condensation with 2 : 3-dibromopropaldehyde and 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI), and (b) by reaction with the salt (XLII; X = Br), prepared from (XLI) and the quaternary compound derived from pyridine and 2 : 3-dibromopropaldehyde. Full details^{45, 46} and additional methods have since been reported. (c) R. B. Angier *et al.*,⁵³ have condensed reductone with *p*-aminobenzoyl-L-glutamic acid to give a stable intermediate (XLIII) which was isolated and then allowed to react with 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI)



to yield the vitamin (XLIV). (d) Another method devised by the same group of workers⁵⁴ involves bromination of 2-amino-6-hydroxy-8-methyl-

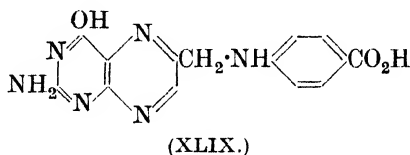
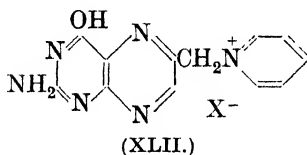
⁵¹ A. L. Franklin, E. L. R. Stokstad, M. Belt, and T. H. Jukes, *J. Biol. Chem.*, 1947, **169**, 427.

⁵² R. Lewisohn, C. Leuchtenberger, R. Leuchtenberger, and J. C. Keresztesy, *Science*, 1946, **104**, 436.

⁵³ R. B. Angier, E. L. R. Stokstad, J. H. Mowat, B. L. Hutchings, J. H. Boothe, C. W. Waller, J. Semb, Y. SubbaRow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, junr., *J. Amer. Chem. Soc.*, 1948, **70**, 25.

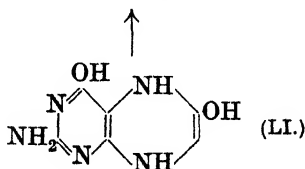
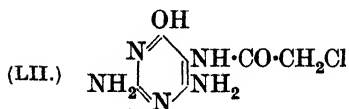
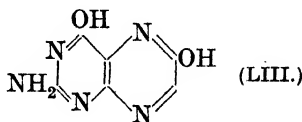
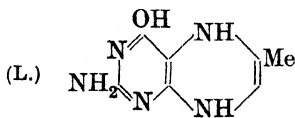
⁵⁴ J. H. Boothe, C. W. Waller, E. L. R. Stokstad, B. L. Hutchings, J. H. Mowat, R. B. Angier, J. Semb, Y. SubbaRow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, junr., *ibid.*, p. 27.

pteridine (XLV; R = Me) to the 8-bromomethyl derivative (XLV; R = CH₂Br), followed by condensation with diethyl *p*-aminobenzoylglutamate (XLVI), and subsequent hydrolysis of the ester groups. Neither of the routes (c) and (d) appears to be so satisfactory as route (a), however. Recently, the suggestions were made that bromomethylglyoxal acetal (XLVII) and the oxime (XLVIII) (prepared from acraldehyde and either nitrosyl chloride or amyl nitrite and hydrochloric acid) may be substituted for 2 : 3-dibromopropaldehyde.⁵⁵



Racemic vitamin B₆ has been synthesised by route (a),⁴⁵ employing, of course, *p*-aminobenzoyl-DL-glutamic acid. The simpler pteric acid (XLIX), which has active anti-anæmia properties, has been synthesised from (XLI) and *p*-aminobenzoic acid by routes (a),⁴⁵ (b),⁴⁶ and (c),⁵³ though in the last case the crude product was not purified. The same applies to further methods for pteric acid⁵⁶ and vitamin B₆⁵⁷ involving the use of reductone. Other crude products shown to possess microbiological activity were preparations by route (c) of ethyl pteroate and the diethyl ester of vitamin B₆.⁵³

Reduced Pteridines.—A 7 : 10-dihydropteridine was obtained⁵⁴ in the course of preparing the intermediate (XLV; R = Me), the preferred method on the large scale being reduction of the 6-methylpyridinium iodide (XLII; X = I) with zinc and alkali. The 7 : 10-dihydro-product (L) was readily oxidised to the aromatic form (XLV; R = Me) by treatment with hydrogen peroxide, iodine, or potassium permanganate.



A new synthesis of 7 : 10-dihydroxanthopterin (LI) has been effected by reaction of 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI) with chloroacetic

⁵⁵ U.S.P. 2,436,073; 2,444,005.

⁵⁶ P. Karrer and R. Schwyzer, *Helv. Chim. Acta*, 1948, **31**, 777.

⁵⁷ H. S. Forrest and J. Walker, *Nature*, 1948, **161**, 721.

acid, yielding the 5-chloroacetamido-derivative (LII) which was then cyclised by heating to 85° with sodium hydrogen carbonate solution.⁵⁸ Conversion of the product (LI) into xanthopterin (LIII) was achieved by catalytic oxidation. Some related 7:8-dihydropteridines are evidently considerably less stable for, as noted by J. C. E. Simpson,⁴¹ dihydro-derivatives which undergo *in situ* oxidation are intermediates in the preparation of vitamin B₆ (or of pteric acid) by routes (a) and (b), above. It is somewhat surprising that routes (c) and (d), which lead to the aromatic form directly, do not give better yields.

The catalytic hydrogenation of vitamin B₆ has been studied by B. L. O'Dell and his collaborators.⁵⁹ In dilute sodium hydroxide over platinum a dihydropteroylglutamic acid is formed, which the authors suggest is the 9:10-dihydro-compound, whilst in glacial acetic acid the reduction yields a tetrahydro-derivative. Both products show an ultra-violet absorption maximum at 2900 Å., and both are easily re-oxidised (in the air) to the parent compound. It is tentatively suggested that vitamin B₆ may function, like riboflavin, as a hydrogen acceptor in oxidation-reduction enzyme systems.^{59a}

The Fermentation *L. casei* Factor.—Preliminary reports concerning this factor, already outlined in these reviews,⁴¹ have also been substantiated by the disclosure of full details. The fermentation *L. casei* factor is produced in aerobic cultures of *Corynebacterium* sp. on a synthetic medium, and is isolated,⁶⁰ in similar fashion to the liver *L. casei* factor,⁴⁷ by adsorption on norite A followed by elution with aqueous ethanol, and purification through the barium salt and the methyl ester. Anaerobic hydrolysis⁴² of the purified fermentation factor afforded an amine fraction (shown to consist of 2 mols. of an α -amino-dicarboxylic acid) and a crystalline substance which appeared from its ultra-violet absorption spectrum to be identical with the liver *L. casei* factor (vitamin B₆). On biological assay, however, the product showed only 57—58% of the expected activity. Subsequently it was realised that the material might be a racemate. This was confirmed⁴⁵ by a comparison of the infra-red absorption spectrum of the degradation product with that of synthetic racemic vitamin B₆, which demonstrated their identity. It was not concluded from this result that the fermentation factor is a derivative of racemic liver factor, but that racemisation occurs during the hydrolysis. Cleavage of the fermentation *L. casei* factor with sulphurous acid afforded⁴³ 2-amino-6-hydroxypteridine-8-aldehyde (XLV; R = CHO) [converted into a mixture of (XLV; R = Me) and (XLV; R = CO₂H) by alkali] and a tetrapeptide, comprised of one molecule of *p*-aminobenzoic acid and three molecules of glutamic acid. That the linkage between pteridine and peptide portions was entirely through the amino-group of the

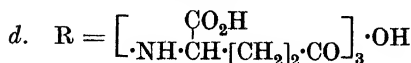
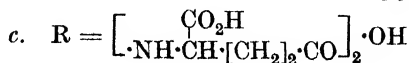
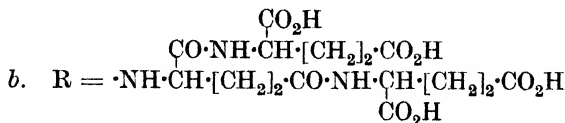
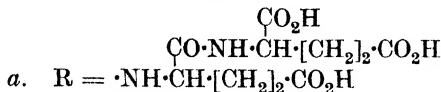
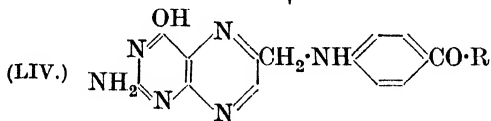
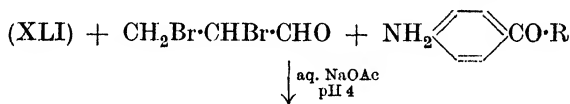
⁵⁸ U.S.P. 2,437,853.

⁵⁹ B. L. O'Dell, J. M. Vandenbelt, E. S. Bloom, and J. J. Pfiffner, *J. Amer. Chem. Soc.*, 1947, **69**, 250.

^{59a} Cf. ref. 129 quoted in ref. 41.

⁶⁰ B. L. Hutchings, E. L. R. Stokstad, N. Bohonos, N. H. Sloane, and Y. SubbaRow, *J. Amer. Chem. Soc.*, 1948, **70**, 1.

p-aminobenzoic acid moiety was confirmed⁴² by the equivalent rates of appearance of 2-amino-6-hydroxypteridine-8-carboxylic acid (XLV; R = CO₂H) and aromatic amine during aerobic alkaline hydrolysis. Anaerobic alkaline hydrolysis gave (XLV; R = Me). Proof of the structures of the pteridine degradation products (XLV)^{44, 41} and of the liver *L. casei* factor as pteroyl-L-glutamic acid,^{45, 46, 53, 54} by synthesis, taken together with other results summarised above, strongly indicated that the fermentation *L. casei* factor was a peptide derived from the combination of a pteroyl-glutamyl moiety with two molecules of glutamic acid. It only remained to determine the precise arrangement of the residues comprising the glutamic acid tripeptide portion of the molecule, five structural isomers being possible. This has been done by synthesising some of the variants and also related compounds, rather than by examining the tetrapeptide fragment from the sulphurous acid degradation. The first preparations to be reported⁶¹ in detail were of *N*-(α -pteroamido- γ -carboxybutyryl)glutamic acid (originally named pteroyl- α -glutamylglutamic acid) (LIVa) and pteroylglutamyl-diglutamic acid (originally named pteroyl- $\alpha\gamma$ -glutamyl diglutamic acid) (LIVb), the former being isolated in a pure state. The methods employed were extensions of the best route previously used for the synthesis of the liver *L. casei* factor, namely reaction of 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI) and 2 : 3-dibromopropaldehyde with the appropriate *p*-amino-benzoyl peptide (prepared by standard methods from L-glutamic acid) :



Neither of the products (LIVa) and (LIVb) showed any significant micro-biological activity, making it at once apparent that the isomer (LIVb) was

⁶¹ J. H. Mowat, B. L. Hutchings, R. B. Angier, E. L. R. Stokstad, J. H. Boothe, C. W. Waller, J. Semb, and Y. SubbaRow, *J. Amer. Chem. Soc.*, 1948, **70**, 1096.

not identical with the fermentation *L. casei* factor. Subsequently *N*-(γ -pteroamido- γ -carboxybutyryl)glutamic acid (originally named pteroyl- γ -glutamylglutamic acid) (LIVc) was prepared and isolated,⁶² and found to possess 60–70% of the growth promoting activity of pteroylglutamic acid for *L. casei* or *Streptococcus faecalis* R. Synthesis of a second isomer of pteroyltriglutamic acid, containing so-called γ -glutamyl linkings, was then attempted *via* the tetraethyl ester of the peptide (LIVd), and in this way a preparation was obtained^{63, 62} containing *N*-[γ -(γ' -pteroamido- γ' -carboxybutyramido)- γ -carboxybutyryl]glutamic acid (originally named pteroyl- γ -L-glutamyl- γ -L-glutamyl-L-glutamic acid) (LIVd), a compound which has been termed⁶³ teropterin. On microbiological assay the crude material showed the same ratio of activity for the two test organisms as the fermentation *L. casei* factor. Unfortunately the synthesis proved unsuitable for the large scale preparation of teropterin, and insufficient material was obtained for complete purification and characterisation. Nevertheless, the microbiological results are obviously sufficiently specific for it to be claimed that a synthesis of the fermentation *L. casei* factor has been accomplished, and that the structure of this factor is that of teropterin (LIVd). Final proof by the isolation of a pure product from alternative syntheses is awaited with interest.

Broad analogies might suggest that the heptaglutamic acid peptide portion of the vitamin B₆ conjugate molecule is also a linear γ -peptide, but as yet there is no real evidence concerning this point.

Rhizopterin.—A factor capable of supporting the growth of *S. lactis* R on a "folic acid" deficient medium, but inactive for *L. casei*, had early been recognised,⁶⁴ and named the S.L.R. factor.⁶⁵ E. L. Rickes, L. Chaiet, and J. C. Keresztesy⁶⁶ have now described in detail the isolation procedure which, starting from a charcoal adsorbate obtained during the purification of *Rhizopus nigra* fumaric acid fermentation liquors,⁶⁷ involves a 200,000-fold concentration, achieved by re-adsorption on charcoal and fuller's earth, precipitation from solution, and chromatography on alumina. The crystalline growth factor thus isolated was recognised from its analysis (C₁₅H₁₂O₄N₆) and properties (insolubility, m. p. >300°, absorption spectrum, titration behaviour that of a dibasic acid) to be a pterin, and it was accordingly renamed rhizopterin. Treatment of rhizopterin with alkali resulted in loss of the *S. lactis* R activity, and from acid and alkali hydrolysates a weaker dibasic acid, *aporphizopterin* (C₁₄H₁₂O₃N₆), was obtained.⁶⁸ This product exhibited ultra-violet absorption characteristics closely similar to those of vitamin B₆ (pteroylglutamic acid). Working with rhizopterin

⁶² J. H. Boothe, J. H. Mowat, B. L. Hutchings, R. B. Angier, C. W. Waller, E. L. R. Stokstad, J. Semb, A. L. Gazzola, and Y. SubbaRow, *J. Amer. Chem. Soc.*, 1948, **70**, 1099.

⁶³ *Idem*, *Trans. N.Y. Acad. Sci.*, 1948, **10**, 70.

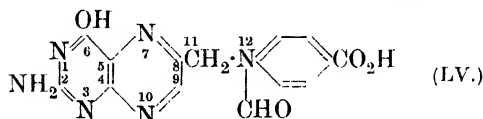
⁶⁴ J. C. Keresztesy, E. L. Rickes, and J. L. Stokes, *Science*, 1943, **97**, 465.

⁶⁵ J. L. Stokes, J. C. Keresztesy, and J. W. Foster, *ibid.*, 1944, **100**, 522.

⁶⁶ *J. Amer. Chem. Soc.*, 1947, **69**, 2749. ⁶⁷ U.S.P. 2,327,191.

⁶⁸ E. L. Rickes, N. R. Trenner, J. B. Conn, and J. C. Keresztesy, *J. Amer. Chem. Soc.*, 1947, **69**, 2751.

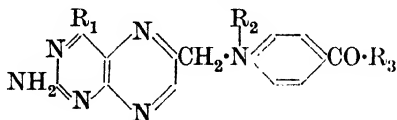
purified through its *luetoethylenediaminocobaltic* salt, D. E. Wolf and his co-workers⁶⁹ extended the foregoing results by obtaining chemical evidence of its pterin nature, and came to the conclusion that *aporphizopterin* was identical with pteric acid (XLIX), a conclusion substantiated by biological assay against *S. faecalis*. *apoRhizopterin* on oxidation with potassium chlorate in hydrochloric acid afforded oxalylguanidine and chloranil. Similar degradation of benzoylrhizopterin gave benzoylguanidine and chloranil, whilst pyrolysis or drastic hydrolysis of rhizopterin gave *p*-aminobenzoic acid. The formation of benzoylguanidine from benzoylrhizopterin had, of course, shown that the amino-group in the 2-position of the pteridine ring was unsubstituted in rhizopterin. The formation of a "deaminorhizopterin" ($C_{15}H_{11}O_5N_5$) on treatment of rhizopterin with nitrous acid pointed to the same conclusion. Finally, with the recognition of formic acid as the second product of mild hydrolysis of rhizopterin to *aporphizopterin*, it became clear that rhizopterin had the structure of 12-formylpterioic acid (IV).



This structure was fully confirmed by synthesis: on formylation, both *aporphizopterin* and synthetic pteric acid afforded the same product which was identical with natural rhizopterin.

Vitamin B₆ Antagonists.—In the present connection, antagonist implies a pteridine derivative which reverses, competitively, the growth-promoting activity of natural pterin factors for various micro-organisms. The possible usefulness of such compounds has already received mention: this usefulness would, of course, depend on the inhibition of microbial-growth being paralleled by anæmia-producing effects in higher animals.

The following antagonists have all been prepared by method (a) (see earlier) from the appropriate 4:5-diaminopyrimidine, *p*-aminobenzoyl compound, and 2:3-dibromopropaldehyde:



| | R ₁ | R ₂ | R ₃ |
|------------------------|-----------------|----------------|---|
| (i) ⁷⁰ | OH | H | L-NH·CH(CO ₂ H)·CH ₂ CO ₂ H |
| (ii) ^{71, 72} | NH ₂ | H | L-NH·CH(CO ₂ H)·[CH ₂] ₂ ·CO ₂ H |
| (iii) ⁷² | NH ₂ | H | OH |
| (iv) ^{72, 73} | OH | Me | OH |
| (v) ⁷² | NH ₂ | Me | OH |
| (vi) ^{72, 73} | OH | Me | L-NH·CH(CO ₂ H)·[CH ₂] ₂ ·CO ₂ H |
| (vii) ⁷² | NH ₂ | Me | L-NH·CH(CO ₂ H)·[CH ₂] ₂ ·CO ₂ H |
| (viii) ⁷³ | OH | Et | OH |
| (ix) ⁷³ | OH | Bu | OH |

The last two compounds and some further derivatives, not listed, were not purified completely since they proved unpromising. Of the remainder, pteroylaspartic acid (i) and 6-aminopteroylglutamic acid (ii) are particularly powerful antagonists, the former being reported ⁷⁰ to inhibit the utilisation by *L. casei* of pterotic acid, vitamin B₆ (LIVc), and the fermentation *L. casei* factor (LIVd). The acid (ii) has marked physiological effects on rats, chicks, and humans.^{72a} A further antagonist has been prepared by the reaction of 2:4:5-diamino-6-hydroxypyrimidine and *p*-aminobenzoyl-L-glutamic acid with 2:3-dibromobutyraldehyde, but the structure of the product, described as "9-methylfolic acid," has not been rigidly proved.^{74*} The structure of (iv) was determined ⁷³ by permanganate oxidation to the known 2-amino-6-hydroxypteridine-8-carboxylic acid: cleavage did not occur on aerobic alkaline hydrolysis in contrast to the behaviour of pterotic acid.⁴⁵ Some simpler pteridines having amino-groups in both the 2- and the 6-position, prepared by M. F. Mallette *et al.*⁷⁵ (see later), are also reported to have antagonistic activity,⁷⁶ exhibiting an antibacterial action not only towards *L. casei* and *S. faecalis* but also towards *L. arabinosus*, which synthesises its own "folic acid." Substitution of hydroxyl for the amino-groups in either the 2- or the 6-position of these compounds result in loss of this activity.

Other Synthetic Pterins.—Further examples have appeared of the preparation of pteridines (LVI) by condensation of 4:5-diaminopyrimidines with α -dicarbonyl compounds. Mallette *et al.*⁷⁵ have condensed the 2:6-dihydroxy- (LVII; R₁ = R₂ = OH), 2-amino-6-hydroxy- (LVIII; R₁ =

⁶⁹ D. E. Wolf, R. C. Anderson, E. A. Kaczka, S. A. Harris, G. E. Arth, P. L. Southwick, R. Mazingo, and K. Folkers, *J. Amer. Chem. Soc.*, 1947, **69**, 2753.

⁷⁰ B. L. Hutchings, J. H. Mowat, J. J. Oleson, E. L. R. Stokstad, J. H. Boothe, C. W. Waller, R. B. Angier, J. Semb, and Y. SubbaRow, *J. Biol. Chem.*, 1947, **170**, 323.

⁷¹ D. R. Seeger, J. M. Smith, junr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1947, **69**, 2567.

⁷² J. M. Smith, junr., D. B. Cosulich, M. E. Hultquist, and D. R. Seeger, *Trans. N.Y. Acad. Sci.*, 1948, **10**, 82.

^{72a} J. J. Oleson, B. L. Hutchings, and Y. S. SubbaRow, *J. Biol. Chem.*, 1948, **175**, 359; S. Farber, L. K. Diamond, R. D. Mercer, R. F. Sylvester, junr., and J. A. Wolff, *New England J. Med.*, 1948, **238**, 787.

⁷³ D. B. Cosulich and J. M. Smith, junr., *J. Amer. Chem. Soc.*, 1948, **70**, 1922.

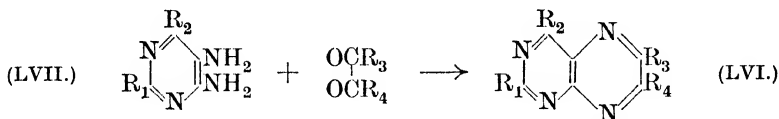
⁷⁴ G. J. Martin, L. Tolman, and J. Moss, *Arch. Biochem.*, 1947, **12**, 318; *Science*, 1947, **106**, 168.

⁷⁵ M. F. Mallette, E. C. Taylor, junr., and C. K. Cain, *J. Amer. Chem. Soc.*, 1947, **69**, 1814.

⁷⁶ L. J. Daniel, L. C. Norris, M. L. Scott, and G. F. Heuser, *J. Biol. Chem.*, 1947, **169**, 689.

* A suggestion (M. Gordon, J. M. Ravel, R. E. Eakin, and W. Shive, *J. Amer. Chem. Soc.*, 1948, **70**, 878) that pteroyl derivatives function as carriers of formate (cf. the structure of rhizopterin) in the biosynthesis of purines, possibly being involved in the insertion of a single carbon unit into the pyrimidine ring, must be regarded with extreme caution since the evidence adduced in its support consists of microbiological experiments with this "methylfolic acid." Later work (W. Shive, J. M. Ravel, and R. E. Eakin, *ibid.*, p. 2614; W. Shive, J. M. Ravel, and W. M. Harding, *J. Biol. Chem.*, 1948, **176**, 991) seems to afford no substantiation.

NH_2 , $\text{R}_2 = \text{OH}$), and 2 : 6-diamino- (LVII; $\text{R}_1 = \text{R}_2 = \text{NH}_2$) derivatives with glyoxal and diacetyl, and in addition, by reaction of the latter pyrimidine with benzil, phenanthraquinone, and acenaphthaquinone, have prepared a series of symmetrically 8 : 9-disubstituted pteridines :



W. Steinbuch ⁷⁷ condensed (LVII; $\text{R}_1 = \text{R}_2 = \text{NH}_2$) with mesoxalic ester and saponified the product to obtain 6-aminoisoxanthopterincarboxylic acid (LVI; $\text{R}_1 = \text{R}_2 = \text{NH}_2$, $\text{R}_3 = \text{CO}_2\text{H}$, $\text{R}_4 = \text{OH}$). A similar reaction with (LVII; $\text{R}_1 = \text{R}_2 = \text{OH}$) provided the hitherto inadequately described deaminoisoxanthopterincarboxylic acid (LVI; $\text{R}_1 = \text{R}_2 = \text{R}_4 = \text{OH}$; $\text{R}_3 = \text{CO}_2\text{H}$). It is to be noted incidentally that the nomenclature of some of these products could be improved. Diacetyl, phenanthraquinone, and acenaphthaquinone have also been condensed with 4 : 5-diamino-6-hydroxy-2-ethylthiopyrimidine (LVII; $\text{R}_1 = \text{SEt}$, $\text{R}_2 = \text{OH}$) to give three new 2-ethylthiopteridines (LVI; $\text{R}_1 = \text{SEt}$, $\text{R}_2 = \text{OH}$). 6 : 8 : 9-Trihydroxy-2-mercaptopteridine was prepared by G. B. Elion *et al.*⁷⁸ from the mercaptopyrimidine (LVII; $\text{R}_1 = \text{SH}$, $\text{R}_2 = \text{OH}$) and oxalic acid. These workers found also that, contrary to the results of O. Islay,⁷⁹ reduction of 2-chloro-5-nitro-4-aminopyrimidine can be effected by an excess of alcoholic potassium hydrogen sulphide to yield 4 : 5-diamino-2-mercaptopyrimidine (LVII; $\text{R}_1 = \text{SH}$, $\text{R}_2 = \text{H}$). Condensation of the latter with glyoxal then afforded 2-mercaptopteridine (LVI; $\text{R}_1 = \text{SH}$, $\text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$) itself.

A number of aminohydroxypteridine mono- and di-carboxylic acids and methyl esters (LVI; $\text{R}_1 = \text{OH}$ or NH_2 , $\text{R}_2 = \text{OH}$ or NH_2 , $\text{R}_3 = \text{H}$, CO_2Me , or CO_2H , $\text{R}_4 = \text{CO}_2\text{Me}$ or CO_2H) have been prepared by C. K. Cain and his collaborators⁸⁰ for testing as microbial growth factors and for studies on growth and haemoglobin formation in chicks. The acids were obtained from the corresponding (known) 9-methyl- ($\text{R}_3 = \text{H}$, $\text{R}_4 = \text{Me}$) and 8 : 9-dimethyl- ($\text{R}_3 = \text{R}_4 = \text{Me}$) pteridines by oxidation in alkaline solution with potassium permanganate, and were converted into the methyl esters with methanolic hydrogen chloride. It was observed that a carboxyl group in the 8-position is less stable than in the 9-position of the pteridine nucleus, for on heating the 8 : 9-dicarboxylic acid (LVI; $\text{R}_1 = \text{R}_2 = \text{OH}$, $\text{R}_3 = \text{R}_4 = \text{CO}_2\text{H}$) in quinoline monodecarboxylation to the 9-carboxylic acid (LVI; $\text{R}_1 = \text{R}_2 = \text{OH}$, $\text{R}_3 = \text{H}$, $\text{R}_4 = \text{CO}_2\text{H}$) took place.

The potentialities of sugars and related compounds for the synthesis of pteridines from 4 : 5-diaminopyrimidines have been investigated by P. Karrer

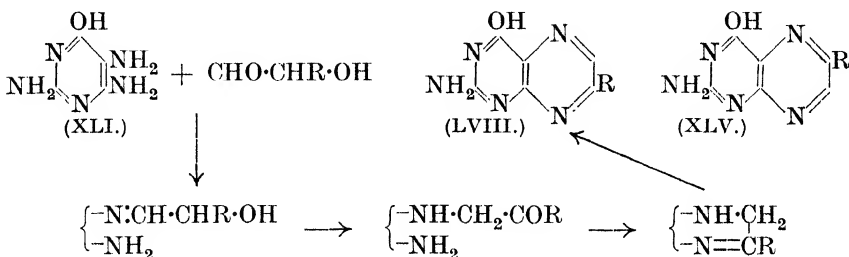
⁷⁷ *Helv. Chim. Acta*, 1948, **31**, 2051.

⁷⁸ G. B. Elion and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553.

⁷⁹ *Ber.*, 1906, **39**, 250.

⁸⁰ C. K. Cain, M. F. Mallette, and E. C. Taylor, junr., *J. Amer. Chem. Soc.*, 1948, **70**, 3026.

and his co-workers.⁸¹ By performing the reaction under carbon dioxide in boiling water containing a little acetic acid, pteridines were prepared from 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI) and the aldoses, arabinose, xylose, glucose, galactose, and glyceraldehyde. The configuration of the products was not at first rigidly established, but it was suggested that they were probably 9-hydroxyalkylpteridines (LVIII) (*e.g.*, $R = CH_2 \cdot OH$ in the case of reaction with glyceraldehyde) formed in the following way :



The ketose, fructose, gave a different product from glucose, so that, on the preceding ideas, it was formulated as the isomeric 2-amino-6-hydroxy-8-D-*arabotetrahydroxybutyl*pteridine (XLV; $R = [CH \cdot OH]_3 \cdot CH_2 \cdot OH$). The spectra of the pteridines from glucose and glyceraldehyde were closely similar to one another, but differed from the spectra of the products from fructose and dihydroxyacetone.

H. G. Petering and D. I. Weisblat⁸² in a preliminary report stated, in agreement, that under Karrer's conditions D-glucose reacts with (XLI) to form the 9-D-*arabotetrahydroxybutyl*pteridine (LVIII; $R = [CH \cdot OH]_3 \cdot CH_2 \cdot OH$), whereas D-glucosone at pH 5—9 yields mainly the 8-isomer. These authors found in addition that in strongly acid solution both these two reactions proceeded in the opposite senses since mixtures were obtained richer in the isomer of the product previously isolated (*i.e.*, glucose gave the 8-isomer; glucosone the 9-isomer).

Following up their initial experiments, Karrer and Schwyzer⁵⁶ substantiated their ideas that aldoses condensed with the pyrimidine (XLI) to yield 9-substituted pteridines, whereas ketoses gave the 8-isomers. Thus it was shown that the product from (XLI) and dihydroxyacetone [evidently (XLV; $R = CH_2 \cdot OH$)] when condensed with *p*-aminobenzoyl-L-glutamic acid afforded a product containing 15% of vitamin B₆ (an 8-substituted pteridine). A similar reaction with the 9-hydroxymethylpteridine derived from (XLI) and glyceraldehyde, on the other hand, gave rise to no micro-biological activity, though a modification in which (XLI), *p*-aminobenzoyl-L-glutamic acid, and glyceraldehyde ditoluene-*p*-sulphonate were condensed in the presence of potassium iodide led to a product containing 6% of the vitamin.

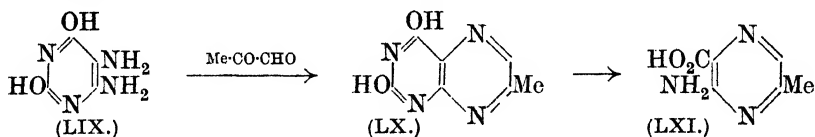
⁸¹ P. Karrer, R. Schwyzer, B. Erden, and A. Siegwart, *Helv. Chim. Acta*, 1947, 30, 1031.

⁸² *J. Amer. Chem. Soc.*, 1947, 69, 2566.

Independently of Karrer *et al.*, H. S. Forrest and J. Walker⁸³ had treated D-glucose and D-fructose with 2 : 4 : 5-triamino-6-hydroxypyrimidine and obtained from each condensation the same product, which they suggested was probably 2-amino-6-hydroxy-8-D-arabotetrahydroxybutylpteridine (XLV; $R = [CH \cdot OH]_3 \cdot CH_2 \cdot OH$). However, P. Karrer and R. Schwyzer⁸⁴ pointed out that the reaction conditions involved the presence of phenylhydrazine. Since glucose and fructose both give the same phenyl-osazone, it was to be expected that under such conditions the same pteridine would arise from each sugar. There was no doubt that in the absence of phenylhydrazine different products were formed.

Since in the structural determination of the liver *L. casei* factor the 8- and 9-methyl- and -carboxy-pteridines, (XLV; $R = Me$ and CO_2H) and (LVIII; $R = Me$ and CO_2H), were prepared and characterised unambiguously,⁴⁴ it will in future be a simple matter to orientate pteridine products which arise from ambiguous condensations. Thus Forrest and Walker⁵⁷ have shown that the product from reaction of 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI) with reductone and methyl *p*-aminobenzoate is mainly pterioic ester (an 8-substituted pteridine) since aerobic alkaline hydrolysis yielded 2-amino-6-hydroxypteridine-8-carboxylic acid (XLV; $R = CO_2H$). Independently, H. J. Backer and A. C. Houtmann⁸⁵ had suggested that the reaction between reductone and the same pyrimidine (XLI) produced the 9-hydroxymethylpteridine (LVIII; $R = CH_2 \cdot OH$) by analogy with the behaviour of methylglyoxal. Clearly though, analogies are unreliable in this field.

The condensation of methylglyoxal with 4 : 5-diamino-2 : 6-dihydroxypyrimidine (LIX) had earlier been shown by J. Weijlard *et al.*⁸⁶ to yield only 2 : 6-dihydroxy-9-methylpteridine (LX), since degradation gave none of the known 2-amino-5-methylpyrazine. Subsequently, Cain *et al.*⁸⁰ have confirmed the structure (LX) in a more positive manner by degrading the substance to the known 2-amino-3-carboxy-6-methylpyrazine (LXI):



In this connection it is of interest that pyruvic acid condenses with 2 : 4 : 5-triamino-6-hydroxypyrimidine to yield both of the theoretically possible products :⁷⁸



⁸³ *Nature*, 1948, **161**, 308.

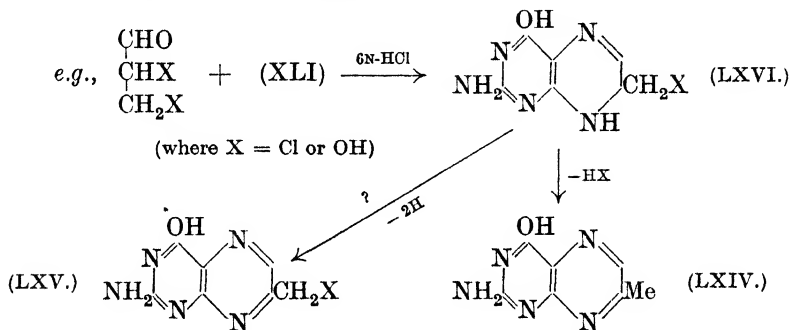
⁸⁴ *Helv. Chim. Acta*, 1948, **31**, 782.

⁸⁵ *Rec. Trav. chim.*, 1948, **67**, 280.

⁸⁶ J. Weijlard, M. Tishler, and A. E. Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.

In boiling 2*N*-sulphuric acid 9-methylxanthopterin (LXII) is formed, whilst in dilute acetic acid a mixture results, containing 8-methylisoxanthopterin (LXIII). This behaviour is comparable with that of glucosone (see earlier).

Recently, the variously-reported preparations of hydroxymethylpteridines have been questioned. According to R. B. Angier and his co-workers⁸⁷ the condensations in 6*N*-hydrochloric acid of glyceraldehyde, *s*-dichloroacetone, 2 : 3-dichloropropaldehyde (cf. reaction of the dibromo-compound at pH 4), and α -bromotetronic acid (presumed to hydrolyse to 1-bromo-3-hydroxypropan-2-one) with 2 : 4 : 5-triamino-6-hydroxypyrimidine (XLI) all lead to 2-amino-6-hydroxy-9-methylpteridine (LXIV), and not to the expected 9-hydroxymethyl or -halogenomethyl compounds (LXV). Similarly ethyl α -dibromoacetoacetate reacts with (XLI) to give, after treatment with alkali, 2-amino-6-hydroxypteridine-8-acetic acid (XLV; R = CH₂·CO₂H) instead of a bromo- or hydroxy-acetic acid derivative. It is suggested that intermediately-formed dihydropteridines such as (LXVI) aromatised by loss of the elements of water or hydrogen halide (as the case may be) rather than by dehydrogenation :



There is, however, the possibility that under certain conditions oxidation of the dihydro-intermediate (LXVI) might take place preferentially, and a substituted-methylpteridine (LXV) would then result. Further work is obviously required: especially is it desirable that better analyses be obtained for the alleged hydroxymethyl compounds. In view of the further reactions which have been achieved with these products there can be little doubt that they are not pure methylpteridines, but their precise nature, *e.g.*, whether they are mixtures containing (LXV) and/or (LXVI), is in need of clarification.

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J. A. ELVIDGE.

J. D. LOUDON.

S. H. HARPER.

J. F. W. McOMIE.

D. H. HEY.

B. C. SAUNDERS.

B. JONES.

⁸⁷ R. B. Angier, C. W. Waller, J. H. Boothe, J. H. Mowat, J. Semb, B. L. Hutchings, E. L. R. Stokstad, and Y. SubbaRow, *J. Amer. Chem. Soc.*, 1948, **70**, 3029.

BIOCHEMISTRY.

1. INTRODUCTION.

BIOCHEMISTRY is at present enjoying a period of unprecedented effluorescence. So many and so varied are the fronts upon which knowledge in the subject is advancing that it is difficult to make a selection for articles such as those presented in these Annual Reports. A choice has nevertheless been made which it is hoped will illustrate the progress being achieved within the subject itself and also in that region of contact between biochemistry and pathology to which chemotherapy belongs.

Advances in technique have frequently served as a powerful weapon and incentive—as in partition chromatography and the study of protein structure reviewed below—but seldom, if ever, has the adoption of a method of experimentation proved so revealing or so altered the established ways of thought in a science as has the use of isotopes in biochemistry. The realisation of a dynamic equilibrium embracing the constituents of even highly differentiated structural tissues such as bone has proved startling indeed. But not only that. Products such as uric acid, found in the excreta, were formerly regarded as end stages of a series of chemical changes affecting more complex body or food constituents from which source they originated. Now, however, the realisation is borne in upon us that molecules such as those of uric acid are being continually synthesised from relatively very simple units, and continually broken down again. There is an overall equilibrium, but the dynamic exchange is far more intense and deep-seated than could have been realised without the use of labelled atoms. More and more significance is being attached to the part played by small molecules in the biochemical exchanges of the cell.

It used also to be thought and taught that, the more precise the information obtained concerning the detail of chemical reactions occurring in the body, the more nearly were these seen to simulate happenings in the test tube. Oxidation by dehydrogenation is a case in point. But the use of isotopes has revealed reactions of carbon dioxide fixation and mechanisms for the synthesis of such materials as the tricarboxylic acids for which there is no *in vitro* parallel. Elegant and beautiful in their achievement, they appear also to be of fundamental importance in the life of the cell.

In directing attention to the lines of approach which are being explored toward a chemotherapeutic control of tuberculosis, the intention has been to emphasise a point too frequently overlooked: that it is the host-tissue relationship which dominates the picture, the more particularly perhaps in this infectious disease than in others, and that the situation is one which chemotherapy dare not afford to neglect and may even be able to exploit advantageously in particular cases.

The outstanding successes of chemotherapy have up to the present

been very largely results of happy accident, but it is possibly no exaggeration to say that the era of rational approach, based upon a detailed knowledge of the biochemistry of both host and parasite, should hold incomparably brighter promise for the future.

C. R.

2. THE FUNCTION OF SMALL MOLECULES IN BIOSYNTHESIS.

With the greatly increased availability of stable and radioactive isotopes, their use is becoming less of a matter for the specialist laboratory. Many books ¹ and reviews ² are now available which describe and discuss the various techniques used in tracer studies. In this Report, methods as such will not be discussed; but rather an attempt will be made to discuss some recent work, largely but by no means exclusively carried out with tracers, which both indicates and influences the present trends of biochemical thought.

Investigations with isotopes have helped to develop our ideas in three broad directions. An almost immediate result of the extensive use of deuterium and ¹⁵N by the Columbia school was the concept of the "dynamic state" of many body constituents. Cell components, such as proteins and fats, were shown to be in a state of continuous degradation and re-synthesis—a view which contrasts sharply with those generally held before 1935. Referring to fat depots, R. Schoenheimer³ was able to say that "contrary to the general idea of the slow metabolism of fat tissues, all the experiments . . . point to the fact that the fat stores are very actively involved in the conversion processes characteristic of life." Such experiments have abundantly justified and confirmed Hopkins's far-sighted dictum—"life is a dynamic equilibrium in a polyphasic system."

A second development of the continued use of isotopic tracers led to the identification of specific precursors involved in biosyntheses under normal physiological conditions. Now that investigations have been extended to cover many cell components, it becomes apparent that the living organism very often makes use of relatively simple chemical units for biosynthesis. For example, a compound such as carbon dioxide, formerly considered almost exclusively as an end product, takes part in a large variety of bio-

¹ "Radioactive Tracers in Biology," M. D. Kamen, Academic Press Inc., 1947; "Symposium on the Use of Isotopes in Biological Research," American Cancer Society, 1947; "The Use of Isotopes in Biology and Medicine," University of Wisconsin Press, 1948; "Radioactive Indicators, Their Application in Biochemistry, Animal Physiology, and Pathology," G. Hevesy, Interscience Publishers Inc., 1948; "Preparation and Measurement of Isotopes and Some of their Medical Aspects," Supplement, U.S. Naval Medical Bulletin, March—April, 1948; "Preparation and Measurement of Isotopic Tracers," D. W. Wilson (Editor), J. W. Edwards, Ann Arbor, 1946.

² D. Rittenberg and D. Shemin, "Currents in Biochemical Research," 1946, p. 261; M. D. Kamen, *Ann. Rev. Biochem.*, 1947, **16**, 631; J. Sacks, *Chem. Reviews*, 1948, **42**, 411; B. Vennesland, *Adv. Biol. Med. Physics*, 1948, **1**, 45; N. S. Radin, *Nucleonics*, 1947, **1**, No. 1, 24; No. 2, 48; No. 4, 51; 1948, **2**, No. 1, 50; No. 2, 33.

³ Harvey Lectures, 1937, 142.

synthetic reactions; or a compound such as uric acid, apparently an excretory product derived from a particular group of related substances, may also be continuously synthesised from very simple units. In contrast to their normal chemical properties, these small molecules frequently exhibit a remarkable lability in the living cell, and it is scarcely possible to consider biochemical reactions in terms of formal chemical equations involving relatively stable and identifiable intermediates. At present, it is not possible to specify the actual nature of these highly reactive units. It is possible that they are free radicals; or that they are activated by combination in a high energy bond, or by adsorption on enzyme surfaces. Whilst very similar units may be derived from different sources, such as fat, carbohydrate, or protein, there is evidence to show that they are not identical.

A third concept, the validity of which has been reinforced by isotope studies, is that of group or radical transfer. Many enzyme systems have been discovered which catalyse the transference of a chemical unit from one molecule to another. These transfer processes are possible with amino- and amidino-groups, methyl groups, acetyl groups, phosphate radicals, and hydrogen atoms. The importance of such reactions has, for example, been appreciated in nutrition studies, and a supply of labile methyl groups is recognised to be essential for full growth. Further transfer reactions may be discovered, and this type of reaction seems to be widely used in synthetic processes.

The general outlines of biosynthesis as they are at present understood may be summarised as follows. The breakdown of tissue and dietary components, in addition to providing energy, furnishes a "pool" of metabolites, from which tissue components may be regenerated and excretory products are derived. The metabolic "pool" has no physical reality, but may be pictured in terms of the availability of newly formed small molecules. These small molecules, if isolated from tissues, would in general be stable compounds. In the cell, and in the presence of specific enzymes (themselves also presumably involved in the general dynamic state), the organic molecule becomes an activated component of the dynamic processes of life. It will become part of a chain of continuous reactions (which are frequently cyclic and mutually dependent) in which almost all body components, including the so-called storage materials, take part. The function of these active small molecules has been emphasised by K. Bloch: ⁴ "body constituents of high molecular weight are synthesised by condensation of numerous small-sized units rather than by the utilisation and rearrangement of preformed large molecules." Whether a compound such as cholesterol is formed by simultaneous condensation of the necessary C_2 and other units, or whether the synthesis involves a series of precursors of increasing molecular weight, is still a major problem for the biochemist.

The C_1 and C_2 compounds which have been most extensively investigated up to the present time are carbon dioxide, acetic acid, and glycine. Excellent

⁴ *Physiol. Reviews*, 1947, 27, 594.

and comprehensive reviews on carbon dioxide⁵ and acetic acid⁶ have been published, and in this Report only the more recent findings can be discussed. A more complete account on glycine will be given; its function in the biosynthesis of porphyrins and purines will be considered separately, but its more general properties will be first outlined.

The Metabolic Activity of Glycine.

The General Properties of Glycine.—Although the metabolism of most amino-acids has been investigated with isotopes, no single nitrogenous material has yet been found to rival the intense reactivity of glycine in biosyntheses. It seems likely that glycine has a rather special function and is one of the fundamental small units used in biosyntheses. It is known to participate in the biosynthesis of the following compounds: proteins, glutathione, creatine, ornithine, ethanolamine (and hence choline), uric acid, yeast purines, haemoglobin (and possibly stercobilin), glycogen (almost certainly *via* serine), acetate (in *Diplococcus glycinophilus*), and 5(4)-aminoglyoxaline-4(5)-carboxyamide. Glycine can act as a detoxicant (*e.g.*, in the formation of hippuric acid and nicotinylglycine), and there is substantial evidence for the conversion of glycine into serine and proline in yeast.

The ready incorporation of administered glycine (labelled with ¹⁵N) into the tissue proteins of animals was first observed almost ten years ago by Ratner *et al.*⁷ It was also shown, in these early studies, that labelled glycine was specifically utilised for the sarcosine moiety of creatine,⁸ and that glycine nitrogen was the precursor of the α - and δ -amino-groups of ornithine.⁹

The peptide, glutathione, of liver and intestine was found to incorporate ¹⁵N from glycine more readily than did the proteins of the same tissues.¹⁰ Recently, the *in vitro* uptake of glycine into the glutathione of isolated liver has been studied.¹¹ About 0.1–0.2 mg. of glycine was incorporated per hour per g. of liver, and a similar uptake was observed with acetylglycine. In these *in vitro* experiments an uptake of ¹⁵N into the liver proteins was also observed, thus confirming earlier observations with radio-methionine,¹² and ¹⁴CO₂,¹³ that proteins themselves can be regenerated by liver tissue *in vitro*. The *in vitro* uptake of ¹⁴C from glycine (labelled in the carboxyl

⁵ H. G. Wood, *Physiol. Reviews*, 1946, **26**, 198.

⁶ K. Bloch, *ibid.*, 1947, **27**, 574.

⁷ S. Ratner, D. Rittenberg, A. S. Keston, and R. Shoenheimer, *J. Biol. Chem.*, 1940, **134**, 665.

⁸ K. Bloch and R. Shoenheimer, *ibid.*, 1940, **133**, 633.

⁹ D. Shemin and D. Rittenberg, *ibid.*, 1944, **153**, 401; 1945, **158**, 71.

¹⁰ H. Waelsch and D. Rittenberg, *ibid.*, 1941, **139**, 761.

¹¹ K. Bloch and H. S. Anker, *ibid.*, 1947, **169**, 765.

¹² J. B. Melchior and H. Tarver, *Arch. Biochem.*, 1947, **12**, 309.

¹³ C. B. Anfinsen, A. Beloff, A. B. Hastings, and A. K. Solomon, *J. Biol. Chem.*, 1947, **168**, 771.

and methylene groups) has been studied in rat tissue homogenates¹⁴ by Greenberg and his co-workers. Their experimental work, particularly with respect to possible contamination of the isolated materials, seems open to some objections.

From studies on ¹⁴C uptake from glycine by the rat foetus Greenberg *et al.* have concluded that growth is the result of an increased activity of protein synthesis.¹⁵ On the other hand, D. Rittenberg and D. Shemin¹⁶ have suggested that the greater overall anabolic rate during growth is a result of a relative decrease of degradative processes. In experiments by Rittenberg and Shemin to test their hypothesis, rats were given a standard amount of ¹⁵N glycine after removal of about half of the liver.¹⁷ The rate of protein formation in the regenerating liver was not appreciably faster than that in normal animals. They concluded that in this case growth was a result of the inhibition of degradative reactions.

The mechanism of peptide bond synthesis has been extensively studied, and, now that an *in vitro* regeneration of protein has been observed, further work will probably follow. The nature of the activated intermediates involved is still almost completely unknown. A study of the related model synthesis of *p*-aminohippuric acid from *p*-aminobenzoic acid and glycine in rat liver slices has shown that this reaction is dependent on energy-yielding processes.¹⁸ Evidence for this dependence was the stimulating effect of cytochrome *c* on the aerobic reaction, and the fact that under anaerobic conditions the reaction could be supported by the addition of ATP. These results strongly suggest that phosphorylated intermediates are involved in this synthesis. No evidence has yet been obtained either to prove or to disprove the suggestion of D. Rittenberg and D. Shemin¹⁹ that peptide synthesis may proceed *via* an acetylated intermediate. An interesting observation is the easy *in-vitro* formation of hippuric acid by reaction of dibenzoyl hydrogen phosphate with glycine.²⁰ Sodium dibenzoyl phosphate was more resistant to hydrolysis than the monobenzoyl compound, but the latter compound did not react with glycine under the "physiological conditions" employed (pH 7.4, 37°). With sodium dibenzoyl phosphate and glycine, half of the anhydride groups disappeared within a few minutes; the reaction has also been observed with ornithine and lysine. It was suggested that diacyl phosphates (or substituted derivatives) rather than monoacyl phosphates could be the intermediate activated precursors of peptide bond synthesis.

Evidence for the participation of glycine in the biosynthesis of serine

¹⁴ F. Friedberg, T. Winnick, and D. M. Greenberg, *J. Biol. Chem.*, 1947, **171**, 441.

¹⁵ F. Friedberg, M. P. Schulman, and D. M. Greenberg, *ibid.*, 1948, **173**, 437.

¹⁶ "Currents in Biochemical Research," 1946, 272.

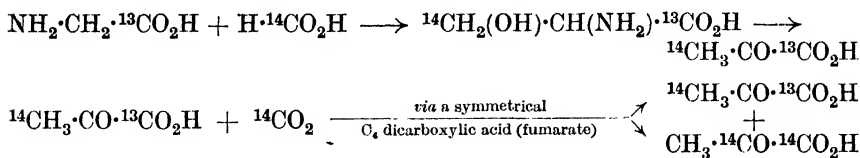
¹⁷ D. Rittenberg, E. E. Sproul, and D. Shemin, *Fed. Proc.*, 1948, **7**, 180.

¹⁸ P. P. Cohen and R. W. McGilvery, *J. Biol. Chem.*, 1946, **166**, 261; 1947, **169**, 119; 1947, **171**, 121.

¹⁹ *Ann. Rev. Biochem.*, 1946, **15**, 247.

²⁰ H. Chantrenne, *Nature*, 1947, **160**, 603; *Compt. rend. Trav. Lab. Carlsberg*, 1948, **26**, 297.

and proline in yeast has been provided by Ehrensvärd and his colleagues.²¹ *Torulopsis utilis* was grown with either DL-alanine or glycine (both labelled as $^{13}\text{CO}_2\text{H}$) as the sole carbon source. With DL-alanine, the ^{13}C was rather evenly distributed amongst the various amino-acids, with an expected marked excess only in the alanine fraction. With glycine, however, ^{13}C was transferred predominantly to the serine and proline fractions. This is a reversal of the well-known serine \rightarrow glycine reaction, and it is possible that the proline may be formed analogously to the pyrrole ring of porphyrins (*q.v.*). There is also evidence for the *in vitro* conversion of glycine ($\text{NH}_2\cdot^{14}\text{CH}_2\cdot\text{CO}_2\text{H}$) into serine in rat-liver homogenate.²² Experiments on the formation of glycogen from glycine have now confirmed that an *in vivo* conversion of glycine into serine can take place. Earlier experiments in which $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$ was fed to mice, showed that about 1% of the isotope was incorporated into liver glycogen.²³ Glycine is believed not to be deaminated to acetic acid in animal tissues (see p. 251), and it was suggested that glycine was incorporated into glycogen by a mechanism involving successive conversion into serine and pyruvate. Very substantial evidence that these reactions do take place was provided by the simultaneous administration of $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$ and $\text{H}\cdot^{14}\text{CO}_2\text{H}$ to a rat.²⁴ Glycogen and serine were isolated and degraded so that individual carbon atoms could be identified. Serine contained ^{13}C only in the carboxyl group; and ^{14}C almost exclusively in the β -position. Glycogen contained ^{13}C only in the 3 and 4 positions, and to almost the same extent as the serine carboxyl. ^{14}C was present in all the glycogen carbon atoms, but the specific activity in the 1 and 6 positions was more than twice that of the 3 and 4 positions. These distributions agree with the initial formation of pyruvate from serine, followed by its reversible transformation to a symmetrical C_4 dicarboxylic acid (for full details, see the paper by H. G. Wood, N. Lifson, and V. Lorber²⁵):



Hence there is a pathway for the conversion of glycine and formate into glycogen *via* serine and pyruvate. (The reactivity of formate is of considerable interest. Its incorporation into uric acid was previously the first well-authenticated case of an animal biosynthesis involving formate. It is possible that further work will show it to be utilised in other directions.)

Although glycine is believed not to be deaminated to acetic acid in

²¹ G. Ehrensvärd, E. Sperber, E. Saluste, L. Reis, and R. Stjärnholm, *J. Biol. Chem.*, 1947, **169**, 759.

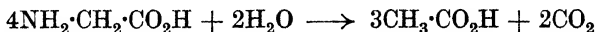
²² T. Winnick, I. Moring-Claesson, and D. M. Greenberg, *ibid.*, 1948, **175**, 127.

²³ N. S. Olsen, A. Hemingway, and A. O. Nier, *ibid.*, 1943, **148**, 611.

²⁴ W. Sakami, *ibid.*, 1948, **176**, 995.

²⁵ *Ibid.*, 1945, **159**, 475.

animal tissues, its anaerobic decomposition by *Diplococcus glycinophilus* does lead to the accumulation of acetic acid : *



The reaction has been investigated with carboxyl- and methylene-labelled (^{14}C) glycine, $^{14}\text{CO}_2$, and $\text{CH}_3\cdot^{14}\text{CO}_2\text{H}$.²⁶ The following conclusions were reached. (a) 75% of the acetate methyl group and 54% of the acetate carboxyl carbon are derived from the glycine methylene group; 90–95% of the carbon dioxide evolved is derived from the glycine carboxyl group. The main reaction, therefore, is probably a condensation of two glycine molecules through their methylene groups with either simultaneous or subsequent decarboxylation. Direct reduction of glycine is also unlikely since 6% of the acetate methyl carbon and 38% of the acetate carboxyl carbon are derived from $^{14}\text{CO}_2$. (b) Complete oxidation of glycine takes place to a small extent only, and the acetate is subsequently metabolised only slowly (if at all). This probably rules out a mechanism which involves $^{14}\text{CO}_2$ fixation *via* pyruvate and oxaloacetate (with a subsequent regeneration of acetic acid).

The Oxidation of Glycine.—As S. Ratner, V. Nocito, and D. E. Green have pointed out,²⁷ the oxidation of glycine and the nature of its breakdown products in the body are not well understood.

In two experiments, $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$ has been used to obtain information about this problem. Administration of the labelled glycine to mice was followed by a 50% excretion of the ^{13}C in respiratory CO_2 within 16 hours.²³ The same compound, however, was not decarboxylated in isolated mammalian heart preparations.²⁸

The apparent resistance of glycine to oxidation in tissue-slice experiments has often been observed. Ratner *et al.*²⁷ have now described a glycine oxidase, present in the liver and kidney of all the animals examined, which catalysed the aerobic oxidation of glycine. The preparation contained

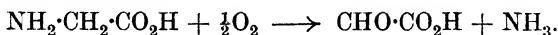
²⁶ H. A. Barker, B. E. Volcani, and B. P. Cardon, *J. Biol. Chem.*, 1948, **173**, 804.

²⁷ *Ibid.*, 1944, **152**, 119.

²⁸ V. Lorber and N. S. Olsen, *Proc. Soc. Exp. Biol. Med.*, 1946, **61**, 227.

* *Note added in proof*: By feeding $\text{NH}_2\cdot^{14}\text{CH}_2\cdot\text{CO}_2\text{H}$ to rats, D. B. Sprinson (*J. Biol. Chem.*, 1949, **178**, 529) has shown that the methylene carbon atom of glycine can be utilised in the formation of both acetic acid and aspartic acid. In the acetate, both carbon atoms were derived from the labelled atom in glycine; in the aspartate, the α - and β -carbon atoms were 2.5 times as active as the carboxyl groups—which were probably derived from respiratory carbon dioxide. Two mechanisms were suggested. (a) Formation of glyoxylic acid, followed by condensation with glycine to a C_4 compound in equilibrium with aspartate. (b) Degradation of glycine to a labelled formic acid (or near derivative) and condensation of this with more glycine to $\alpha\beta$ -labelled serine. Hence it was converted into pyruvate to acetate and oxaloacetate. W. Sakami (*ibid.*, p. 519) has provided evidence that the latter mechanism can operate in the rat. Feeding $\text{NH}_2\cdot^{14}\text{CH}_2\cdot\text{CO}_2\text{H}$ to rats gave liver-serine containing ^{14}C in both α - and β -carbon atoms. There was almost as much ^{14}C in the β - as in the α -position, and under these conditions glycine was therefore a major source of formate.

flavin adenine dinucleotide as co-enzyme; the oxidation products were glyoxylic acid and ammonia :



In tissue slice experiments (particularly with kidney slices) a rapid formation of oxalic acid from glyoxylic acid was observed.

The Biosynthesis and Metabolism of Purines.—Tracer studies of the synthesis of pyrimidines and purines have again emphasised the important direct participation of small molecules in the biosynthesis of more complex compounds.

The careful experiments of H. Ackroyd and F. G. Hopkins²⁹ had led to the conclusion that histidine and arginine were purine precursors. These amino-acids were removed from the diet of young rats for some weeks during which time the allantoin excretion decreased to 40–50% of its original value. Restoration of one or both amino-acids to the diet brought back the allantoin excretion almost to its original value. With no intention of belittling this work, the following quotation from their paper will emphasise the changes which have taken place in biochemical thought. "When an animal is in a state of full nutrition, it does not follow that such a process as the synthesis of the purine ring would necessarily be much accelerated or increased by mere increase in the supply of its raw material. The accepted distinction between endogenous and exogenous metabolism and the recognised relative constancy of the former could scarcely hold were this the case. We know, it is true, that a large increase of protein in the diet does affect purine metabolism; but an individual amino-acid fed in excess of the immediate current needs of the tissues, as when it is added to an already efficient dietary, will almost certainly be broken down on more direct lines, even if it be a normal precursor of the purine (or other) synthesis in the body."

The results to be discussed have shown that some of the purine nitrogen is derived from a general metabolic pool, and that there are also a number of specific precursors for purine synthesis. On feeding ammonium citrate (labelled with ¹⁵N) to pigeons and rats, there was a rapid incorporation of ¹⁵N into the purines (adenine and guanine) and pyrimidines (thymine and cytosine) of the nucleic acids in internal organs, excretory uric acid, and allantoin;³⁰ the liver incorporated isotope more actively than the other organs. Since nitrogen can be derived therefore from a general pool, purine excretion is not reduced by restricting dietary nitrogen to protein sources. This observation also corroborates the conversion of the nitrogen of amino-acids into purines. In these experiments the pigeon did not utilise urea for purine synthesis. The uptake of ¹⁵N by histidine, in rats, was confined to the α-amino-group, strongly suggesting that its glyoxaline ring was not involved in purine synthesis. (Later studies have shown conclusively that

²⁹ *Biochem. J.*, 1916, **10**, 551.

³⁰ F. W. Barnes and R. Schoenheimer, *J. Biol. Chem.*, 1943, **151**, 123.

³¹ K. Bloch, *ibid.*, 1946, **165**, 477.

labelled L-arginine³² and L-histidine³² are not, in fact, purine precursors.) When guanine was isolated, the 2-amino-group as well as the ring nitrogen were found to have taken up ¹⁵N.

When guanine (containing ¹⁵N in the 2-amino-group, and 1 and 3 nitrogen atoms) was fed to rats, practically no isotope was incorporated into tissue purines or pyrimidines; it was excreted mainly as allantoin, and to an almost insignificant extent as urinary ammonia and urea.³³ Results obtained with pigeons were similar, most of the ¹⁵N being excreted in uric acid. Similarly, the feeding of isotopic pyrimidines (uracil and thymine) to rats produced ¹⁵N only in urinary ammonia and urea; non-incorporation into allantoin excluded the conversion of pyrimidines into purines. Orotic acid (uracil-4-carboxylic acid) has, however, been shown to be a precursor of pyrimidines in the rat, being utilised in the biosynthesis of both uracil and cytosine.^{33a} Recently, G. B. Brown, P. M. Roll, and A. A. Plentl have observed the incorporation of dietary adenine into tissue purines; ³⁴ adenine (labelled with ¹⁵N in the 1 and the 3 position) was fed to rats and was found to be incorporated into nucleic acids, not only in adenine (13.7% replacement of tissue adenine in 4 days) but also guanine (8.2% replacement). ATP contained a small but definite excess of ¹⁵N, and was formed more slowly from dietary adenine. The excreted allantoin contained much more ¹⁵N than the tissue purines, and it is possible that there are separate pathways for the conversion of dietary adenine into tissue purines and excretory allantoin. In confirmation of the earlier experiments, urinary ammonia and urea contained only small amounts of isotope, and the non-incorporation of dietary guanine was again observed by these workers. The reason for this curious discrepancy is obscure, but perhaps guanine is not incorporated because of a specificity of the nuclear membrane. The formation of guanine from adenine took place with retention of the purine skeleton. 2:6-Diaminopurine was postulated by Brown as a possible intermediate in the conversion of adenine into nucleic acid guanine. The compound was synthesised containing ¹⁵N in the 2-amino-group and in the 1 and the 3 position of the ring; it was found to be an effective precursor of guanine in the rat.³⁵

Other experiments have shown that *in vivo* the adenylic acid of skeletal muscle is subject to a very rapid deamination-reamination reaction; ³⁶ ¹⁵N was administered to rats as ammonium citrate, and adenylic acid was isolated. By decomposition with adenylic acid deaminase, it was shown that practically all of the incorporated ¹⁵N was in the 6-amino-group, with little or no ¹⁵N in the ring. The rate of rejuvenation was comparable to

³² C. Tesar and D. Rittenberg, *J. Biol. Chem.*, 1947, **170**, 35.

³³ A. A. Plentl and R. Schoenheimer, *ibid.*, 1944, **153**, 203.

^{33a} S. Bergström, H. Arvidson, E. Hammarsten, N. A. Eliasson, P. Reichard, and H. v. Ubisch, *ibid.*, 1949, **177**, 495.

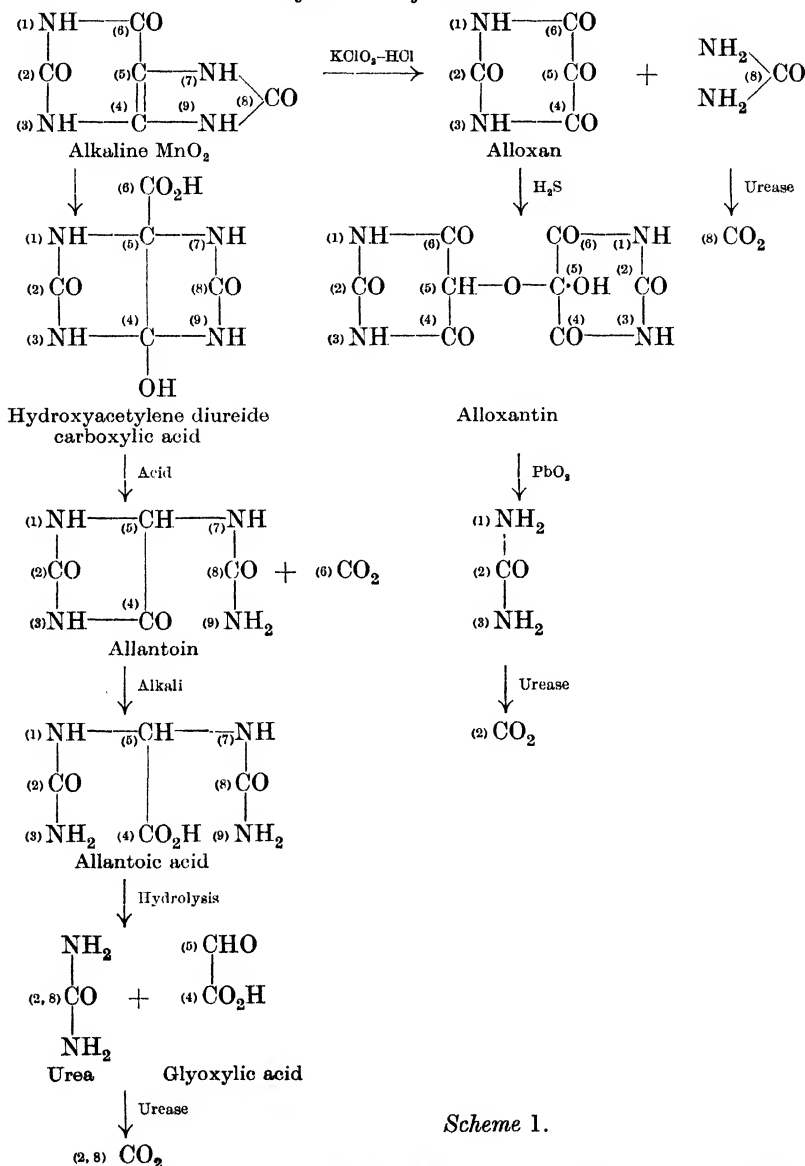
³⁴ *Fed. Proc.*, 1947, **6**, 517.

³⁵ A. Bendich and G. B. Brown, *J. Biol. Chem.*, 1948, **176**, 1471.

³⁶ H. M. Kalckar and D. Rittenberg, *ibid.*, 1947, **170**, 455.

that of the amido-nitrogen of glutamic acid, suggesting that such amides may be involved in the reaction.

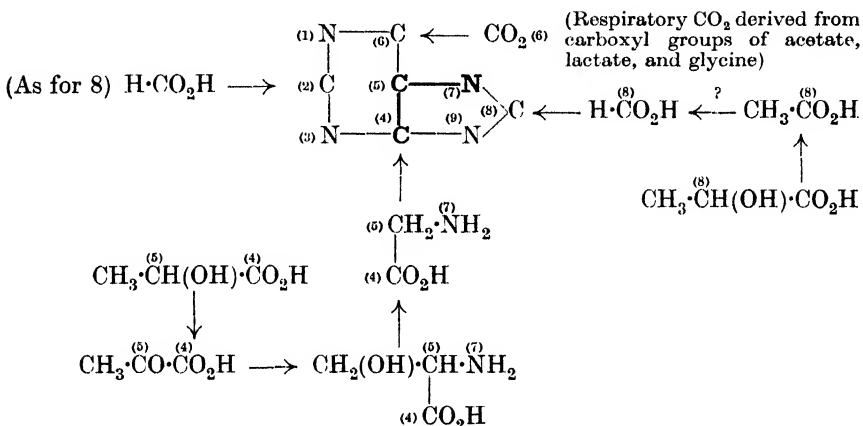
*Degradation of uric acid.*³⁷



Scheme 1.

³⁷ J. C. Sonne, J. M. Buchanan, and A. M. Delluva, *J. Biol. Chem.*, 1946, **166**, 395; J. M. Buchanan and J. C. Sonne, *ibid.*, p. 781; J. C. Sonne, J. M. Buchanan, and A. M. Delluva, *ibid.*, 1948, **173**, 69, 81.

Studies, more especially of the carbon skeleton of uric acid, have shown that a number of other compounds may act as purine precursors; the incorporation of lactate (labelled with ^{13}C in the α - and β -atoms or with ^{13}C in the carboxyl group), $\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$, $\text{H}\cdot^{13}\text{CO}_2\text{H}$, $^{13}\text{CO}_2$, and $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$ into uric acid has been observed in pigeons. By use of the scheme of degradation outlined in Scheme 1, it has been possible to work out the contribution of these compounds to specific atoms of the purine skeleton.³⁷ The following statement and the "reconstructed" uric acid molecule (Scheme 2) summarise the observed facts.



The glycine fragment is indicated by the heavy type. Nitrogen atoms 1, 3, and 9 are from non-specific nitrogen sources.

Scheme 2.

Carbon atoms 2 and 8 :

(i) Both have a common source, and can be derived from the formate carboxyl (72% incorporation), acetate carboxyl (35% incorporation), and the α - (or β -) carbon atom of lactate.

(ii) The incorporation of the lactate carbon atoms probably arises from the fact that they can give rise to acetate carboxyl.

(iii) The relatively higher utilisation of formate suggests that it (or a near derivative) is the direct precursor, and is derived from acetate.

(iv) Carbon dioxide (and lactate carboxyl) are not utilised for these ureide carbons and are not therefore formate precursors (cf. bacteria).

(v) The utilisation of formate in avian metabolism is a notable discovery; very little respiratory $^{13}\text{CO}_2$ was produced from the $\text{H}\cdot^{13}\text{CO}_2\text{H}$.

Carbon atom 6 :

(i) The carboxyl carbons of acetate, lactate, and glycine, as well as carbon dioxide, are incorporated.

(ii) The isotope content of this atom closely parallels that of respiratory

carbon dioxide, indicating that only carbon dioxide is involved in its biosynthesis.

(iii) Formate is not utilised.

Carbon atoms 4 and 5:

(i) Glycine carboxyl is utilised to a large extent for position 4, and lactate carboxyl less so.

(ii) Carbon dioxide, acetate carboxyl, and the α - and β -carbon atoms of lactate are utilised only to a small extent for position 4. The connection with respiratory carbon dioxide indicates utilisation through carbon dioxide.

(iii) Carbon atom 5 is derived from the α - and the β -carbon atom of lactate.

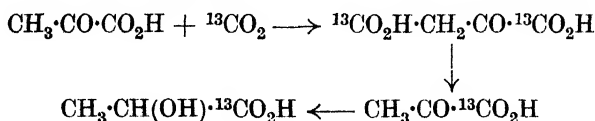
Nitrogen atoms:

The utilisation of the glycine carboxyl (position 4) in conjunction with the results of other experiments, provides evidence that the nitrogen atom of glycine can be utilised for the synthesis of uric acid in pigeons. It has also been shown that the nitrogen of glycine is a specific precursor of uric acid in humans,³⁸ and that it is utilised only for the 7 position. The 1, 3, and 9 nitrogen atoms are derived from a non-specific source. A similar finding has been reported for the guanine derived from yeast nucleic acids.³⁹

It now seems almost certain that the $\overset{(4)}{\text{C}}=\overset{(5)}{\text{C}}-\overset{(7)}{\text{N}}$ unit in uric acid is derived from glycine; the feeding of a doubly labelled glycine would be of value in this connection.

These facts lead to a number of interesting speculations. The role of uric acid is seen to be much more diverse than previously supposed. The utilisation of glycine for uric acid synthesis in both birds and man suggests a connection between its metabolism in these two species. The theory that, in man, uric acid is the main degradation product of complex nitrogenous compounds (particularly purines), and in birds and reptiles the end product of protein metabolism, must be enlarged to include its synthesis, in birds and man, from several small molecules, and its anabolic aspects must be considered equally with its catabolic function.

The conversion of carbon dioxide into uric acid does not appear to take place by any of the known assimilation reactions. The equivalent incorporation of carbon dioxide and the carboxyl carbon atom of lactate (position 6) could have been explained as a result of the well-known reactions:

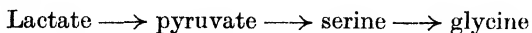


If the possible incorporation of the lactate carbon atoms is considered in terms of such a hypothesis, it can be seen that a 3 carbon chain ($\overset{(6)}{\text{C}}-\overset{(5)}{\text{C}}=\overset{(4)}{\text{C}}$)

³⁸ D. Shemin and D. Rittenberg, *J. Biol. Chem.*, 1947, **167**, 875.

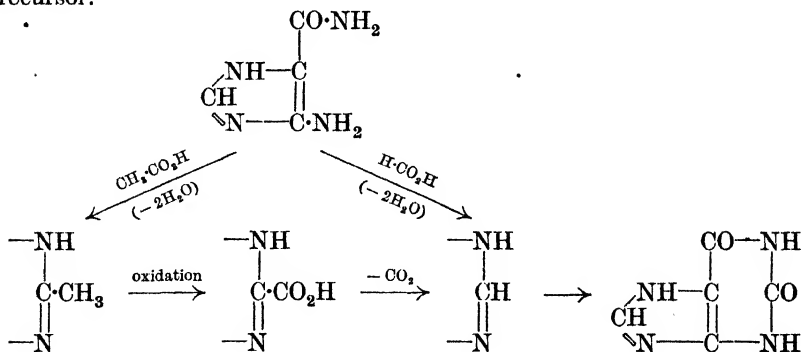
³⁹ R. Abrams, E. Hammarsten, and D. Shemin, *ibid.*, 1948, **173**, 429.

can never be obtained where the carbon atoms are derived from carbon dioxide (6), lactate α -carbon (5), and lactate carboxyl (4). It is suggested that the reactions :



may take place. Serine is a known glycine precursor; and the (reverse) reaction, serine to pyruvate, has been described with *B. coli*, with other bacteria, and in rat liver extract⁴⁰ (see also p. 243). The carboxyl and α -carbon atom of lactate would then become the same atoms of glycine, and this would account for the observed distribution.

The utilisation of formate, and the non-utilisation of carbon dioxide, for the 2 and the 8 carbon atom suggest that a reduced intermediate, *e.g.*, hypoxanthine, may be first formed. Hypoxanthine nitrogen is known to be formed from ammonium salts by pigeon-liver slices, and this synthesis is stimulated by glutamine and oxaloacetic acid.⁴¹ The incorporation of $\text{H}^{14}\text{CO}_2\text{H}$ and $^{14}\text{CO}_2$ into hypoxanthine has been observed in essentially cell-free pigeon-liver homogenates.⁴² The early stages of purine synthesis may involve a condensation of a diamino-compound with formic acid; such a compound may be the diazotisable amine which accumulates in some bacterial cultures undergoing bacteriostasis,⁴³ and which has been identified as 5(4)-aminoglyoxaline-4(5)-carboxyamide.⁴⁴ (Glycine has been shown to be a precursor of this glyoxaline.⁴⁵) Condensation with formate (or acetate) by scheme 3 would complete the purine ring,³⁷ but there is as yet no concrete evidence that the aminoglyoxalinecarboxyamide is the immediate precursor.



Scheme 3.

Recent work^{45a} has, however, shown that dietary hypoxanthine and xanthine (labelled in the 1 and 3 positions with ^{15}N) were ineffective as pre-

⁴⁰ E. Chargaff and D. B. Sprinson, *J. Biol. Chem.*, 1943, **151**, 273.

⁴¹ A. Örstrom, M. Örstrom, and H. A. Krebs, *Biochem. J.*, 1939, **33**, 990.

⁴² G. R. Greenberg, *Arch. Biochem.*, 1948, **19**, 337.

⁴³ M. R. Stetten and C. L. Fox, *J. Biol. Chem.*, 1945, **161**, 333.

⁴⁴ W. Shive *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 725.

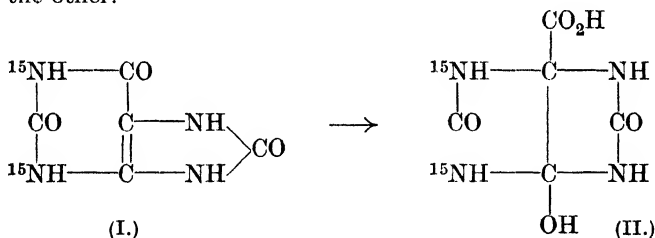
⁴⁵ J. M. Ravel, R. E. Eakin, and W. Shive, *J. Biol. Chem.*, 1948, **172**, 67.

^{45a} H. Getler, P. M. Roll, J. F. Tinker, and G. B. Brown, *ibid.*, 1949, **178**, 259.

cursors of nucleic acids in rats; these compounds were extensively converted into allantoin.

One further conclusion must be mentioned; feeding $\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$ labels the 2 and the 8 carbon atom of uric acid, but not the 4 carbon atom. $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$, however, labels carbon atom 4, but not carbon atom 2 or 8. The carboxyl group of glycine, therefore, cannot be directly utilised in the formation of acetic acid, confirming earlier observations that glycine is glycogenic but acetate is not. As was stated previously this conversion of glycine proceeds *via* serine and pyruvate.

Further Oxidation of Uric Acid.—In most mammals, uric acid is further oxidised to allantoin, and in man a further oxidation can also take place. The enzyme uricase which brings about the first oxidation is widely distributed. It has been shown that an unstable, primary intermediate is first formed which decomposes non-enzymatically in three ways to hydroxy-acetylenediureide, allantoin, and uroxic acid.⁴⁶ Evidence was obtained to show that the intermediate was a symmetrical compound; this has been confirmed by experiments with a labelled uric acid. If the *in vitro* oxidation of uric acid (with ^{15}N at positions 1 and 3) (I) to allantoin takes place *via* the symmetrical intermediate (II), subsequent cleavage of the ring would give allantoin with ^{15}N in the ring in one case, and in the ureide group in the other.



This reaction was carried out,^{47a,b} and the allantoin further degraded (by oxidation to potassium oxonate, or reduction to hydantoin). These products contained the same atom % excess of ^{15}N as the original allantoin, furnishing direct proof that the oxidation to allantoin did involve a symmetrical intermediate such as (II). The oxidation of the uric acid with nitric acid or chlorine gave alloxan with atom % excess of ^{15}N twice that of the parent uric acid. In this case, therefore, there was cleavage only of the glyoxalone ring. When this labelled uric acid was fed to rats, there was again uniform distribution of isotope between the hydantoin and the urea portion of the urinary allantoin.⁴⁸ The *in vivo* oxidation of uric acid does, therefore, proceed *via* a symmetrical intermediate. In this experiment no ^{15}N was found in visceral purines or urea, indicating that there was no degradation of the ingested uric acid to ammonia or urea.

⁴⁶ F. W. Klemperer, *J. Biol. Chem.*, 1945, **160**, 111.

^{47a} L. F. Cavalieri, V. E. Blair, and G. B. Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 1240.

^{47b} L. F. Cavalieri and G. B. Brown, *ibid.*, p. 1242.

⁴⁸ G. B. Brown, P. M. Roll, and L. F. Cavalieri, *J. Biol. Chem.*, 1947, **171**, 835.

The anaerobic breakdown of uric acid by *Clostridium cylindrosporium* yields carbon dioxide, ammonia, acetic acid, and glycine, and the reaction has been studied in the presence of $^{14}\text{CO}_2$.⁴⁹ ^{14}C was incorporated into glycine largely in the carboxyl group, and into acetate, where the methyl group unexpectedly had more than twice the specific activity of the carboxyl group. The low specific activity of the acetate carboxyl group indicated that it was derived largely from the fermented uric acid. The acetate methyl carbon atom and glycine carboxyl group had similar activities and were probably derived entirely from CO_2 . Glycine and acetic acid were evidently formed by different routes.

It is convenient to end this section by referring to some studies of urea. Although the ureide groups of uric acid may be derived from acetic acid, other experiments have shown that $\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$ is not a precursor of urea carbon in the rat.³⁷ These ureide groups therefore have different origins. Early experiments in which liver slices were used, demonstrated that at least 50% of the urea carbon atoms were derived from bicarbonate (CO_2).^{50, 51} In an elegant experiment, it has now been proved that the carbon atom of urea is quantitatively derived from CO_2 . L-Methionine containing ^{14}C in the methyl group was fed to a rat.⁵² It was known that this group was oxidised continuously to CO_2 , and that it therefore continuously labelled the respiratory CO_2 . The latter, and urea, were collected over a 2-day period; reaction of the urea with urease gave CO_2 for analysis. Despite the fact that from the 1st to the 2nd day there was a 35% increase in urea production and a 13% decrease in CO_2 production, the following figures show that there was an exact parallelism between the specific activities of the carbon atoms.

| | Counts per min. per mg. C. | |
|---------------------------------|----------------------------|----------|
| | 1st day. | 2nd day. |
| Respiratory CO_2 | 468 | 106 |
| CO_2 from urea | 465 | 102 |

The incorporation of $^{14}\text{CO}_2$ into the carbonyl group of urea and citrulline has been studied in washed rat-liver residue.⁵³ The fixation into the latter compound was of such a magnitude that citrulline must be considered to be an obligatory intermediate of the Krebs' urea cycle. The conversion of citrulline (containing ^{14}C in the carbonyl group) by liver homogenates gave urea with the same specific activity. In recently reported experiments, the metabolism of ^{14}C labelled urea has been studied after intraperitoneal injection into mice.⁵⁴ The urea was found to have a biological half life period of 5 hours; and all the radioactivity of the urine was due to urea. About 20% of the injected ^{14}C appeared in respiratory CO_2 .

⁴⁹ H. A. Barker and S. R. Elsdon, *J. Biol. Chem.*, 1947, **167**, 619.

⁵⁰ D. Rittenberg and H. Waelsch, *ibid.*, 1940, **136**, 799.

⁵¹ E. A. Evans and L. Slotin, *ibid.*, p. 805.

⁵² C. G. Mackenzie and V. du Vigneaud, *ibid.*, 1948, **172**, 353.

⁵³ S. Grisolia and P. P. Cohen, *ibid.*, 1948, **176**, 929.

⁵⁴ E. Leifer, L. J. Roth, and L. M. Hempelmann, *Science*, 1948, **108**, 748.

Whether this was due to a direct hydrolysis or to a reversal of the urea cycle has not yet been determined.

The Biosynthesis of Porphyrins.—Before 1945 almost the only known fact about porphyrin biosynthesis was that porphyrins could be synthesised from protein derivatives. In 1940, it was stated that “between the absorption of food and the appearance of porphyrins and porphyrin compounds in the cells of the body and in excreta, there lies an unexplored and undoubtedly important gap.”⁵⁵ In 1945, K. Bloch and D. Rittenberg⁵⁶ fed sodium deuterioacetate to rats, and showed that deuterium was incorporated into the hæmin. Since the pyrrole rings of protoporphyrin do not contain ring hydrogen, this was only proof of the participation of acetic acid in side chain formation, but it was the first time that a protoporphyrin precursor had been identified. A little later, D. Shemin and D. Rittenberg⁵⁷ observed, in humans, that glycine could act as a specific nitrogenous precursor of the pyrrole rings in hæmin. Many further results have provided a suggestion of the mechanism of porphyrin biosynthesis.

Shemin and Rittenberg, in this first experiment, fed over a period of 3 days the unprecedented quantity of 66 g. of $^{15}\text{NH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ (containing 32.4 atom % excess of ^{15}N) to a human adult. Blood samples were subsequently withdrawn at intervals, and the ^{15}N content of the isolated hæmin and plasma proteins determined. The ^{15}N content of the hæmin rose rapidly during the first 25 days of the experiment, and then remained practically constant (0.46 atom % excess of ^{15}N) to about the 95th day. The isotope content then declined, following an S-shaped curve. By contrast the isotope concentration of plasma proteins (0.39 atom % excess on the 4th day) had fallen to 0.13 atom % excess by the 30th day.

In further experiments designed to show whether glycine was used specifically, DL-leucine, DL-glutamic acid, and DL-proline (all with ^{15}N in the amino-groups) were fed to rats;⁵⁸ ^{15}N ammonium citrate was also fed for comparison as a non-specific nitrogen source. The last two amino-acids were of particular interest, since they were, on paper at least, possible pyrrole precursors. After allowing for ammonia production from the unnatural isomers of leucine and proline (in the case of glutamic acid no correction was needed since D-glutamic acid is largely excreted), and calculating the results on the basis that the compound fed contained 100% of ^{15}N , the following concentrations were found in the hæmin samples.

| | Hæmin $^{15}\text{N}\%$. |
|------------------------|---------------------------|
| Glycine | 0.93 |
| Ammonium citrate | 0.09 |
| DL-Glutamic acid | 0.17 |
| DL-Proline | 0.18 |
| DL-Leucine | 0.07 |

These results show a direct utilisation of glycine for porphyrin biosynthesis,

⁵⁵ W. J. Turner, *J. Lab. Clin. Med.*, 1940, **26**, 323.

⁵⁶ *J. Biol. Chem.*, 1945, **159**, 45.

⁵⁷ *Ibid.*, p. 567.

⁵⁸ D. Shemin and D. Rittenberg, *ibid.*, 1946, **166**, 621.

the other compounds examined being utilised only non-specifically. It has also been shown that L-histidine is not a porphyrin precursor.³²

The next step was the demonstration that the carboxyl carbon atom of glycine was not utilised for the porphyrin biosynthesis.⁵⁹ When $\text{NH}_2\cdot\text{CH}_2\cdot^{14}\text{CO}_2\text{H}$ was fed to a dog and a rat, no activity was found in the hæm fraction, although there was incorporation into the globin. Subsequent experiments with appropriately labelled glycine ($\text{NH}_2\cdot^{14}\text{CH}_2\cdot\text{CO}_2\text{H}$) showed that the methylene carbon was incorporated.⁶⁰ In this case the specific activity of the isolated hæmin was greater than that of the globin, thus showing that the utilisation was a specific process, independent of the general labelling of biosynthetic intermediates with ^{14}C . After implantation of $\text{Ca}^{14}\text{CO}_3$ pellets in rats, a significant specific activity was found in hæm; ⁶¹ this suggests a utilisation of carbon dioxide for porphyrin biosynthesis, but this evidence can only be regarded as a preliminary indication of such a utilisation.

Further evidence emphasising the importance of small biosynthetic units rather than of large preformed structures has been obtained from experiments with yeast.⁶² When yeast was allowed to autolyse in the presence of ammonium carbonate, a 95-fold increase of porphyrin formation was obtained. The possibility was investigated that porphyrin-containing chromoproteins could be continuously synthesised and then split with excretion of the intact porphyrin (whilst the amino-acid components reached a dynamic equilibrium); but addition of cytochrome *c*, a peroxidase, or catalase did not stimulate porphyrin production, although the compounds added were broken down.

To further the study of porphyrin biosynthesis, work was directed toward finding an active *in vitro* system. The incubation of normal human blood with ^{15}N -labelled glycine was ineffective, but incorporation of glycine into hæm was observed on incubation of nucleated red blood cells (*e.g.*, duck blood).⁶³ A similar *in vitro* hæm synthesis was also observed using blood from people having sickle cell anæmia.⁶⁴ An appreciable uptake of ^{14}C into hæm was later reported on *in vitro* incubation of rabbit bone marrow homogenates with $\text{NH}_2\cdot^{14}\text{CH}_2\cdot\text{CO}_2\text{H}$.⁶⁵

Evidence concerning the relative proportions of glycine involved in the synthesis of each pyrrole ring of porphyrins was obtained by chemical degradation of hæmin obtained after feeding ^{15}N glycine to a human.

⁵⁹ M. Grinstein, M. D. Kamen, and C. V. Moore, *J. Biol. Chem.*, 1948, **174**, 767.

⁶⁰ K. I. Altman, G. W. Casarett, R. E. Masters, T. R. Noonan, and K. Salomon, *ibid.*, 1948, **176**, 319.

⁶¹ W. D. Armstrong, J. Schubert, and A. Lindenbaum, *Proc. Soc. Exp. Biol. Med.*, 1948, **68**, 233.

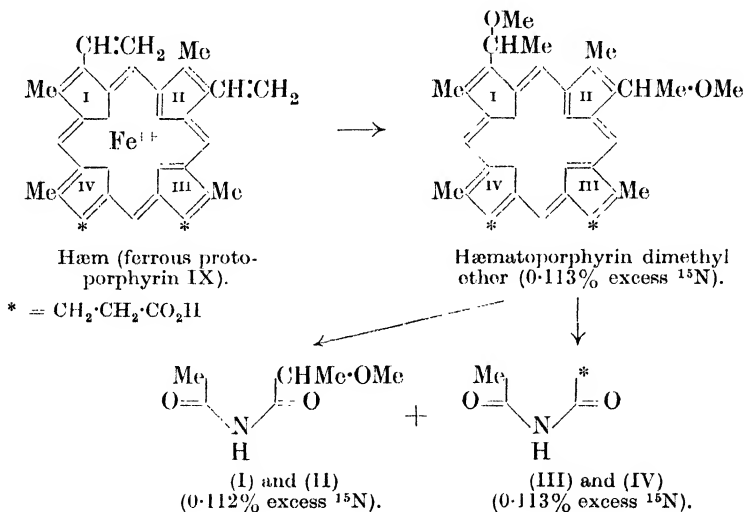
⁶² J. E. Kench and J. F. Wilkinson, *Nature*, 1945, **155**, 579; 1946, **157**, 730; *Biochem. J.*, 1946, **40**, 660.

⁶³ D. Shemin, I. M. London, and D. Rittenberg, *J. Biol. Chem.*, 1948, **173**, 799.

⁶⁴ *Idem*, *ibid.*, p. 797.

⁶⁵ K. I. Altman, K. Salomon, and T. R. Noonan, *ibid.*, 1949, **177**, 489.

Hæmatoporphyrin dimethyl ether was prepared and oxidised to methyl methoxyethylmaleinimide and methyl propionylmaleinimide, a method which gave unequivocal data with respect to the separation and identification of the two different types of pyrrole ring.⁶⁶



The former was derived from rings (I) and (II); the latter from rings (III) and (IV). Their atom % excess of ¹⁵N was identical, and equal to that of the hæmatoporphyrin, showing that glycine was equally utilised in the synthesis of the four pyrrole rings. It is probable that the pyrrole rings are derived from a common precursor. A similar study has been made with the labelled hæmin obtained after the feeding of ¹⁵N glycine to rabbits.⁶⁷ Protoporphyrin methyl ester was prepared, and the vinyl groups reduced with hydrogen. Oxidation of the reduced porphyrin with chromic anhydride gave good yields of methylethylmaleinimide [derived from rings (I) and (II)] and methyl propionylmaleinimide [from rings (III) and (IV)]. Isotope analysis showed that the ¹⁵N content of these two compounds was identical. In this study it was also demonstrated that ¹⁵N ethanolamine was not a direct specific precursor.

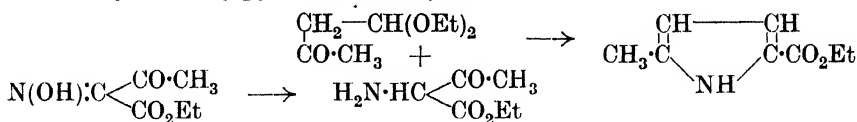
Speculation as to the mechanism by which the α-carbon atom and the nitrogen atom of glycine were used began with the suggestion by Shemin and Rittenberg that glycine was incorporated by initial condensation with a substituted β-keto-aldehyde (which could partly be derived from acetic acid). A formal analogy for this mechanism was provided by H. Fischer and E. Fink's variation of the Knorr pyrrole synthesis.⁶⁸ Reductive con-

⁶⁶ Jonathan Wittenberg and D. Shemin, *Cold Spring Harbor Symp.*, 1948, **13**, 191; *J. Biol. Chem.*, 1949, **178**, 47.

⁶⁷ H. M. Muir and A. Neuberger, *Biochem. Soc. Proc.*, 1948, **43**, lx.

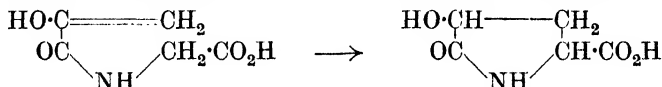
⁶⁸ *Z. physiol. Chem.*, 1944, **280**, 123.

densation of acetoacetaldehyde diethylacetal and oximinoacetoacetic ester led to ethyl 2-methylpyrrole-5-carboxylate :



It was further shown that formylacetone and glycine condensed to yield a product which gave a positive Ehrlich test for pyrroles; the product, however, was not isolated.

Recent observations on the properties of pyruvoylglycine may be of interest for porphyrin biosynthesis. On standing in alkaline solution, pyruvoylglycine underwent an irreversible reaction characterised by the disappearance of the ultra-violet absorption maximum at 2400 Å.⁶⁹ The hygroscopic yellowish-white mass isolated did not have carbonyl properties. The pK of this substance was identical with that of pyrrolidonecarboxylic acid; the structure suggested for this compound was that of a hydroxypyrrolidone carboxylic acid :



The condensation of pyruvic acid with glycine at pH values of 5 to 6.3 has also been investigated, and it was reported that mixtures of various pyrroles were formed.⁷⁰ It is possible that such a condensation, rather than the Fischer-Fink reaction, may be involved in this biosynthesis. It would be of considerable interest to determine whether the carbon atoms of acetate can be used for pyrrole ring formation.

If the porphyrin ring arises by cyclisation of pyrrole units (however these may be formed) two further points must be considered.

(i) Is the non-utilised carbon atom of the glycine (carboxyl group) removed before or after formation of the pyrrole rings? Evidence has been adduced by Altman *et al.*⁶⁰ in favour of the latter hypothesis, but their arguments are open to the following criticisms :

(a) Whilst a glycine decarboxylase is apparently unknown, and glycine resists oxidation in tissue slice experiments, $\text{NH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$ is, in mice, extensively converted to respiratory CO_2 (see discussion, p. 245).

(b) If decarboxylation takes place after pyrrole ring formation the liberated $^{14}\text{CO}_2$ could still be utilised in a subsequent condensation, in the same way as $\text{Ca}^{14}\text{CO}_3$ seems to be used. In fact, the apparent utilisation of $\text{Ca}^{14}\text{CO}_3$, the formation of respiratory CO_2 from glycine, and the non-incorporation of glycine carboxyl, would seem to be contradictory facts.

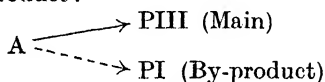
⁶⁹ M. Errera and J. P. Greenstein, *J. Nat. Cancer Inst.*, 1947, **8**, 39.

⁷⁰ A. M. Kuzin and A. P. Guseva, *Biochimia*, 1948, **13**, 27. The structural formula of a compound, given in *Chem. Abs.* (1948, **42**, 7757 b) text, corresponds to an empirical formula $\text{C}_7\text{H}_{13}\text{O}_4\text{N}$; this does not agree with the quoted empirical formula, $\text{C}_8\text{H}_{13}\text{O}_4\text{N}\cdot\text{Ca}$. The original gives analytical data in agreement with the latter empirical formula, but, again, none of the structural formulae proposed seem to agree with the empirical formula. The reaction seems worthy of further investigation.

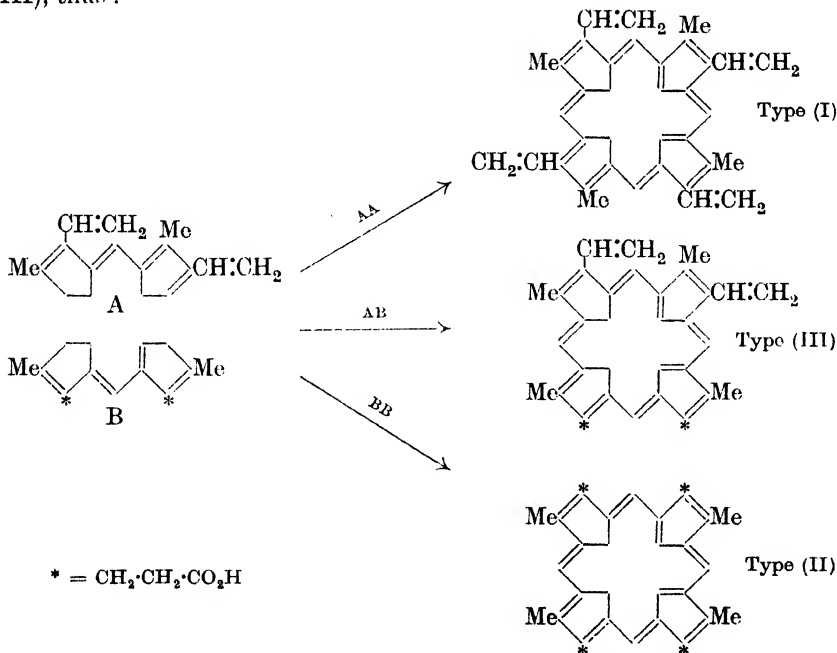
Owing to the relatively slow incorporation of isotope in the experiments with implanted $\text{Ca}^{14}\text{CO}_3$ pellets, the observed uptake into h  min may have been the result of a general labelling of biosynthetic intermediates.

Whilst there is no real evidence to show that decarboxylation takes place after the formation of the pyrrole ring, the suggestion of Altman *et al.* is probably correct.

(ii) What is the mechanism of porphyrin formation from pyrroles? In view of the equivalence of the ring nitrogen atoms, any theory must account for porphyrin synthesis from a common pyrrole precursor, and further give an explanation of the formation of porphyrins of Types (I) and (III). In 1938, C. Rimington postulated that an enzyme system, present in bone marrow, was concerned with a dual synthesis of porphyrins III and I (PIII and PI) from a common precursor (A), and suggested that the events leading to one product were specifically accelerated, making one isomer the main product : ⁷¹



Dobriner *et al.*⁷² pointed out that a combination of two different dipyrromethines (A and B) could give rise to porphyrins of Types (I), (II), and (III), thus :



⁷¹ *Compt. rend. Trav. Lab. Carlsberg, S  r. Chim.*, 1938, **22**, 454.

⁷² K. Dobriner, W. H. Strain, and S. A. Localio, *Proc. Soc. Exp. Biol. Med.*, 1937, **36**, 752; K. Dobriner and C. P. Rhoads, *Physiol. Reviews*, 1940, **20**, 416.

dipyrromethine, such as A, with its mirror image. This would lead to porphyrins of Type (IV); like the Type (II) compounds, these are as yet unknown, and if such mechanisms take place it is necessary to suppose that the enzyme systems cannot handle these compounds.

An alternative to mechanisms of this nature has been proposed by C. Rimington⁷³ on the basis of the decarboxylative condensation of substituted 5-hydroxymethylpyrrole-2-carboxylic acids observed by Siedel and Winkler.⁷⁴ When such compounds were heated alone or in solution, porphyrins were formed in yields of up to 40%.

Whilst these schemes of biosynthesis are almost certainly too mechanistic, and ignore almost completely the function of enzyme systems, they may help to form a picture of porphyrin biosynthesis.

The Life Span of the Human Red Blood Cell.—The study of hæmoglobin synthesis in red blood cells has provided a striking demonstration of a cellular component which is not involved in the dynamic equilibrium of the body. As described earlier, blood samples were withdrawn from a human, for hæmin isolation, after the feeding of a massive amount of $^{15}\text{NH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.⁷⁵ The plot of atom % excess of ^{15}N in the hæmin against time gave a curve very different from that previously observed with any other cellular constituent (*e.g.*, the tissue protein curves). After remaining constant for about 95 days as previously mentioned, the ^{15}N concentration of the hæmin began to decline rather abruptly along an S-shaped curve. This curve has a two-fold significance.

(1) If a cell component does not take part in the dynamic state, a newly synthesised, labelled molecule will remain in the cell, until the cell disintegrates. If indiscriminate cell destruction does not take place, the isotope concentration will reach a maximum value, which will then be maintained at a constant level for a period depending on the life span of the cell. If the isotope is not re-utilised at the time of cell destruction, the isotope concentration of the cells will abruptly decline. This is seen to be the case with the hæmin obtained from red blood cells; inspection of the curve (as well as a precise mathematical analysis) shows the life span of the red blood cell to be about 127 days.

(2) The abrupt decline of the curve shows that the ^{15}N is not re-utilised for hæmoglobin synthesis (in contrast to the iron⁷⁶). It has been shown that a large part of the porphyrin is excreted as stercobilin,⁷⁷ although not all of the stercobilin results from hæmoglobin destruction. In the first few days of the experiment (when labelled red cells were not being destroyed) there was an appreciable concentration of ^{15}N in the stercobilin. A portion of the bile pigment therefore was derived from a source other than the

⁷³ Personal communication.

⁷⁴ W. Siedel and F. Winkler, *Annalen*, 1943, **554**, 162; quoted in FIAT Review of German Science, 1947, Biochemistry, Part 1, p. 132.

⁷⁵ D. Shemin and D. Rittenberg, *J. Biol. Chem.*, 1948, **153**, 401.

⁷⁶ W. O. Cruz, P. F. Hahn, and W. F. Bale, *Amer. J. Physiol.*, 1941–1942, **135**, 595; P. F. Hahn, W. F. Bale, and W. M. Balfour, *ibid.*, p. 600.

⁷⁷ I. M. London, R. West, D. Shemin, and D. Rittenberg, *Fed. Proc.*, 1948, **7**, 169.

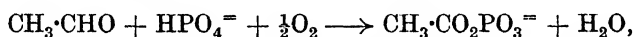
hæmoglobin of mature, circulating, red blood cells. It may be that this incorporation takes place *via* a pyrrole precursor which may form either hæm or stercobilin.

The Function of Acetic Acid.

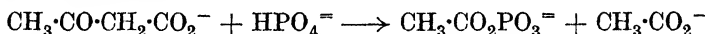
The 1945 Report discussed the nature of the primary oxidation product of pyruvic acid, which in some systems is a highly active C_2 intermediate.⁷⁸ Studies with isotopes have now revealed a high order of activity for acetic acid itself, which has been shown to be a precursor of glycogen, cholesterol, acetoacetic acid, fatty acids, the dicarboxylic amino-acids, protoporphyrin, uric acid, and the acetyl group formed in many acetylation reactions. Acetic acid as a sole carbon source supports almost all *Escherichia* and *Aërobacter* species.⁷⁹

Bloch's excellent review⁴ discusses acetate metabolism in considerable detail, and only a few of the more recent observations can be reported here. The general metabolism of fatty acids will not be discussed.

The Active Form of Acetic Acid.—It is still impossible to specify accurately the nature of the C_2 intermediate (or intermediates), but the increased realisation of the activity of acetate itself suggests that it may be a near derivative of acetic acid. It seems increasingly unlikely that the intermediate is acetyl phosphate, and this compound retains some of its enigmatic character. Acetyl phosphate has been isolated from two new reactions brought about by *Clostridium kluyveri*⁸⁰ (this organism forms hexoic acid from ethanol and acetic acid⁸¹). These are :



and also a phosphoroclastic decomposition of acetoacetate into acetyl phosphate and acetate :



In the early experiments of Lipmann and his colleagues, acetyl phosphate was shown to transfer its phosphate group to glucose in the presence of bacterial enzymes, and a similar transfer has now been observed with a pigeon-liver extract.⁸² It was never possible to demonstrate an acetylating function for acetyl phosphate, although it was observed that acetyl phosphate would acetylate aniline and ammonia in non-enzymic reactions.^{83, 84} A reversal of the initial phosphoroclastic decomposition of pyruvate was demonstrated in *E. coli* preparations by isotope techniques,⁸⁵ but it now appears that this transfer of "acetyl" was, partly at least, not a true

⁷⁸ F. Dickens, *Ann. Reports*, 1945, **42**, 197.

⁷⁹ W. E. Clapper and C. F. Poe, *J. Bact.*, 1947, **53**, 363.

⁸⁰ E. R. Stadtman and H. A. Barker, *J. Biol. Chem.*, 1948, **174**, 1039.

⁸¹ H. A. Barker, M. D. Kamen, and B. T. Bornstein, *Proc. Nat. Acad. Sci.*, 1945, **31**, 373.

⁸² N. O. Kaplan and F. Lipmann, *Fed. Proc.*, 1948, **7**, 163.

⁸³ F. Lipmann, *J. Biol. Chem.*, 1945, **160**, 184.

⁸⁴ R. Bentley, *J. Amer. Chem. Soc.*, 1948, **70**, 2183.

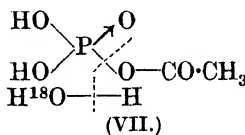
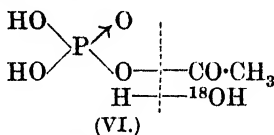
⁸⁵ M. F. Utter, F. Lipmann, and C. H. Werkman, *J. Biol. Chem.*, 1945, **158**, 521.

reversal of the initial reaction. In a further examination of the role of acetyl phosphate, $^{13}\text{CH}_3\cdot\text{CO}_2\text{H}$, $\text{CH}_3\cdot^{13}\text{CO}_2\text{PO}_3\text{H}_2$, and $\text{H}\cdot^{14}\text{CO}_2\text{H}$ were prepared and added to normal pyruvate in the *E. coli* system.⁸⁶ After partial fermentation of the pyruvate the reaction products were lactate and CO_2 [indicating that some of the pyruvate took part in a dismutation reaction: $2\text{CH}_3\cdot\text{CO}\cdot\text{CO}_2\text{H} \longrightarrow \text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H} + \text{CH}_3\cdot\text{CO}_2\text{H} + \text{CO}_2$]. The residual pyruvate was decomposed with yeast carboxylase, so that the carbon atoms could be identified. The carboxyl carbon was found to have a high ^{14}C content (*i.e.*, derived from formate), but the α - and β -carbon atoms did not contain any ^{13}C . In addition $\text{NaH}^{14}\text{CO}_3$ was not significantly fixed under these conditions, so the formate was not first converted into CO_2 . These results indicated that formate was fixed in pyruvic acid without either acetate or acetyl phosphate acting as essential intermediates. It was suggested that the synthetic acetyl phosphate used in these experiments may not have been identical with the biological acetyl phosphate.

The dismutation of pyruvate referred to in the preceding paragraph has been separately studied, and by the use of $\text{NaH}^{13}\text{CO}_3$ and cell free extracts of *Staphylococcus aureus*, it was shown that the reaction was reversible; after the incubation, ^{13}C was found in the carboxyl group of pyruvate.⁸⁷

In further experiments, Lipmann has shown that, with *E. coli* extracts, an "acetyl" transfer took place when acetate was incubated in the presence of added ATP, although acetyl phosphate was quite inactive under these conditions.⁸⁸ In the absence of an acetate acceptor, large amounts of an "acetyl-phosphate-like" compound accumulated. This compound differed from acetyl phosphate in its resistance to a specific muscle acetyl phosphatase, but on standing in acid solutions, even at room temperature, it became indistinguishable from acetyl phosphate; it was not diacetyl phosphate. In dialysed *E. coli* suspensions, the compound (which was free from ATP and contained only traces of other organic phosphates) reacted almost quantitatively with excess of formate to yield pyruvate. Synthetic acetyl phosphate reacted only in the presence of ADP, the former presumably as a phosphate donor.

In a study of the hydrolysis of acetyl phosphate with the use of H_2^{18}O it has been shown that acetyl phosphate splits in alkaline solution with rupture of the C-O bond (VI), and in acid solution with rupture of the P-O bond (VII).⁸⁹

⁸⁶ H. Strecker, L. O. Krampitz, and H. G. Wood, *Fed. Proc.*, 1948, 7, 194.

⁸⁷ T. Wikén, D. Watt, A. G. C. White, and C. H. Werkman, *Arch. Biochem.*, 1947, **14**, 478.

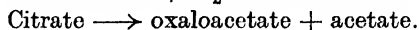
⁸⁸ N. O. Kaplan and F. Lipmann, *J. Biol. Chem.*, 1948, **176**, 459.

¹⁰ R. Bentley, *Cold Spring Harbor Symp.*, 1948, **13**, 15; *J. Amer. Chem. Soc.*, in the press.

The mechanism of acetylation (*e.g.*, of sulphanilamide) in pigeon-liver extracts has been further elucidated by Lipmann's work; the reaction was notably increased by the addition of acetate, and under anaërobic conditions required ATP. It was found that a thermostable component of boiled-liver preparations could be used to reactivate the enzyme system.⁹⁰ This property was traced to the presence, in such extracts, of a coenzyme containing about 10% of pantothenic acid. This coenzyme, named Coenzyme A, was also required by the similar acetylation system for choline in brain.⁹¹ Coenzyme A is a fairly general constituent of living organisms, the highest assays having been recorded in liver, *Clostridium butylicum*, and *Proteus morganii*. The combined pantothenic acid of the Coenzyme A is not available to *L. casei* until after hydrolysis; the acid is apparently bound in the coenzyme by two linkages, one of which is to phosphate.⁹²

The role of pantothenic acid in the metabolism of pyruvate by *Proteus morganii* has also been studied. The stimulation of respiration produced by addition of pantothenic acid to pantothenate-deficient cells could not be accounted for by oxidation of the acetate. When pantothenic acid was absent, acetylmethylcarbinol accumulated, suggesting that a pantothenic acid containing coenzyme was concerned with the utilisation of acetylmethylcarbinol or a related compound.

The *in vitro* synthesis of acetylcholine, mentioned earlier, has been further studied in brain extracts. The acetylation of choline proceeds aërobically in the presence of glucose, lactate, or pyruvate, or anaërobically together with added ATP. Synthesis is in no case stimulated by addition of acetate, thus leaving doubt as to the source of the acetyl group. A number of compounds have been suggested as this source.⁹⁴ A completely soluble enzyme system has been described which in addition to choline and ATP requires the thermostable coenzyme and a substance providing a source of "active acetate." This substance can be citrate, *cis*-aconitate, or acetoacetate, and it was suggested that the active groups were derived as shown :



In continuing his studies on the biosynthesis of cholesterol (about half the carbon atoms of which are derived from acetate) and fatty acids, Bloch has emphasised that the C_2 unit obtained from pyruvate is not the same as that derived from acetic acid, a fact first suggested by their different behaviour in acetylation reactions.⁹⁶ Fatty acid formation can hardly be

⁹⁰ F. Lipmann, *J. Biol. Chem.*, 1945, **160**, 173.

⁹¹ F. Lipmann, N. O. Kaplan, G. D. Novelli, L. C. Tuttle, and B. M. Guirard, *ibid.*, 1947, **167**, 871.

⁹² N. O. Kaplan and F. Lipmann, *ibid.*, 1948, **174**, 37; D. M. Hegsted and F. Lipmann, *ibid.*, p. 89.

⁹³ O. E. McElroy and A. Dorfman, *ibid.*, 1948, **173**, 805.

⁹⁴ D. Nachmansohn and H. M. John, *ibid.*, 1945, **158**, 157.

⁹⁵ M. A. Lipton and E. S. G. Barron, *ibid.*, 1946, **166**, 367.

⁹⁶ K. Bloch and D. Rittenberg, *ibid.*, 1945, **159**, 45.

demonstrated in surviving liver tissue with acetic acid as the only substrate, although under these conditions labelled acetate is rapidly incorporated into cholesterol showing that a biosynthetically active form of acetate is indeed produced.⁹⁷ On the addition of pyruvate and to a lesser extent of oxaloacetate a marked incorporation of acetate into fatty acids takes place; other dicarboxylic acids are ineffective. The interpretation of these results is not yet clear.

The conversion of acetic and butyric acids into liver glycogen has been studied in rats.⁹⁸ When $\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$, $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot^{13}\text{CO}_2\text{H}$, and $\text{CH}_3\cdot^{13}\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ were fed, the isotope distribution in glycogen was similar to that observed when CO_2 was incorporated (*i.e.*, in the 3 and 4 positions of the glucose units). However, when $^{13}\text{CH}_3\cdot\text{CO}_2\text{H}$, $^{13}\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$, and $\text{CH}_3\cdot\text{CH}_2\cdot^{13}\text{CH}_2\cdot\text{CO}_2\text{H}$ were examined, fixation took place in all the fractions obtained on degradation of the glycogen, showing that some incorporation of these acids into glycogen took place by pathways other than those involving CO_2 fixation. The observed isotope distributions were consistent with the following conclusions.

(i) Formation of C_3 fragments from acetate and butyrate *via* the tri-carboxylic acid cycle, and synthesis of glucose units by condensation of two such fragments.

(ii) β -Oxidation of butyrate to 2 molecules of acetate, but not ω -oxidation with the production of succinate.

In early experiments on the oxidation of $\text{CD}_3\cdot\text{CO}_2\text{H}$ by yeast, succinate was obtained containing more excess D than the citrate;⁹⁹ Lynen pointed out that such a distribution was consistent with the assumption that the metabolism took place *via* a tricarboxylic acid cycle.¹⁰⁰ In new experiments, $\text{CH}_3\cdot^{13}\text{CO}_2\text{H}$ was metabolised by yeast; a high ^{13}C concentration was found in cell lipins (the fatty acids contained more ^{13}C than the unsaponifiable material, and the saturated fatty acids 50% more isotope than the unsaturated acids).¹⁰¹ Isotope was incorporated into citrate as shown in the annexed table. On the other hand, during the oxidation of normal acetate

| | ^{13}C excess. | %. |
|---------------------------------|-------------------------|-----|
| Acetate carboxyl | 5.54 | 100 |
| Citrate total | 1.94 | 35 |
| Tertiary carboxyl | 3.16 | 57 |
| Primary carboxyl | 4.42 | 80 |
| Non-carboxyl C | 0.00 | 0 |
| Respiratory CO_2 | 3.11 | 56 |

in presence of $\text{NaH}^{13}\text{CO}_3$ no ^{13}C was found in any product isolated. The last column gives the values calculated on the basis of 100 atom % of ^{13}C

⁹⁷ K. Bloch and W. Kramer, *J. Biol. Chem.*, 1948, **173**, 811.

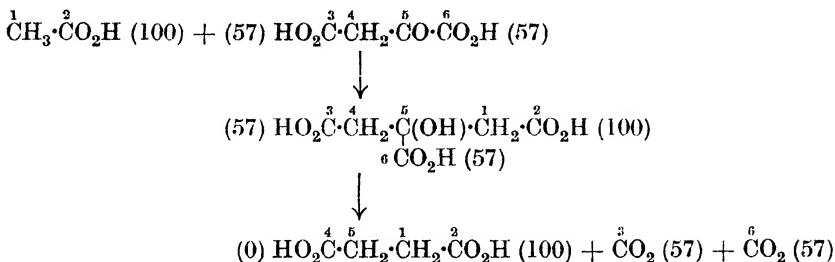
⁹⁸ N. Lifson, V. Lorber, W. Sakami, and H. G. Wood, *ibid.*, 1948, **176**, 1263.

⁹⁹ R. Sonderhoff and H. Thomas, *Annalen*, 1937, **530**, 195.

¹⁰⁰ F. Lynen, *ibid.*, 1943, **554**, 40.

¹⁰¹ S. Weinhouse and R. H. Millington, *J. Amer. Chem. Soc.*, 1947, **69**, 3089.

in the acetate carboxyl; these figures (in parentheses) are consistent with the following scheme :



Any C_4 acid formed in this way by the cycle could have only 50% of acetate ^{13}C in the carboxyl groups. Since the value actually observed was 57%, the authors suggested that there is a supplementary mechanism for the formation of C_4 acids independent of the tricarboxylic acid cycle :



These results therefore were in good agreement with the distribution to be expected if the tricarboxylic acid cycle was involved; it seemed likely that an unsymmetrical C_6 acid, rather than citrate, was the direct participant in the cycle.

In another study of acetate assimilation by yeast (*Saccharomyces cerevisiae*), the following fixations of isotope from $\text{CH}_3\text{-}^{13}\text{CO}_2\text{H}$ (4.33 atom % excess of ^{13}C) were observed ¹⁰² (cf. below). The lactic acid derived from

| | Atom % excess of ^{13}C . |
|-------------------------------------|---------------------------------------|
| Residual acetate | 0.08 |
| Fat | 1.49 |
| Fatty acids..... | 1.14 |
| Lactic acid from glucose | 0.09 |
| Lactate CO_2H | 0.30 |
| " CH_3 | 0.02 |
| " CH-OH | 0.00 |

glucose had ^{13}C only in the carboxyl group, as would be expected if the intact acetate molecule was metabolised, and it was shown that the incorporation was not due to a prior oxidation to CO_2 . Incorporation of acetate into fat was also a result of direct utilisation of the C_2 molecule, without prior conversion into carbohydrate. The optimum conditions for fat synthesis in yeast have been studied by the same authors.¹⁰³

Another study with yeast has been that of the formation of acetyl-methylcarbinol; $^{13}\text{CH}_3\text{-}^{13}\text{CHO}$ was used, and the conclusion made that acetylmethylcarbinol was formed by condensation of pyruvic acid and acetaldehyde.¹⁰⁴

¹⁰² A. G. C. White and C. H. Werkman, *Arch. Biochem.*, 1947, **13**, 27.

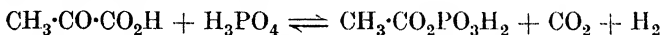
¹⁰³ *Idem, ibid.*, 1948, **17**, 475.

¹⁰⁴ N. H. Gross and C. H. Werkman, *ibid.*, 1947, **15**, 125.

The Utilisation of Carbon Dioxide in Biosynthesis.

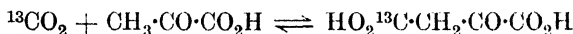
This subject was first reviewed in the Annual Reports for 1941.¹⁰⁵ Since then, other fixation reactions of carbon dioxide have been discovered; these have been reviewed recently by Wood,⁵ and some of the enzymic mechanisms involved have been reviewed by S. Ochoa.¹⁰⁶ In this Report, discoveries since 1946 (the date of Wood's review) will be discussed.

C₂ and C₁ Addition by the Phosphoroclastic Reaction.—The work of J. Wilson, L. O. Krampitz, and C. H. Werkman (cf. Wood, ref. 5, p. 205) has now been published in detail.¹⁰⁷ This constitutes the first demonstration of C₂ and C₁ addition where CO₂ *per se* is the C₁ compound fixed. With *Clostridium butylicum* (in contrast to *E. coli*) formic acid is not an intermediate in the phosphoroclastic reaction:

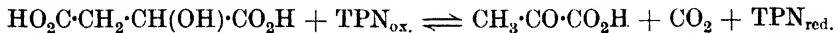


When NaH¹³CO₃ and a buffered enzyme preparation were used, ¹³C was fixed only in the pyruvate carboxyl group, but in the presence of H¹³CO₂H there was no exchange of isotope into the pyruvate. With CH₃·¹³CO₂H there was a very slight exchange, which was significantly greater in the presence of adenylic acid and acetyl phosphate, or on addition of ATP.

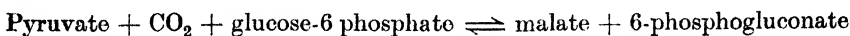
C₃ and C₁ Addition by Oxaloacetate-β-carboxylase.—The original Wood-Werkman reaction was first demonstrated in pigeon-liver extracts by M. F. Utter and H. G. Wood; the reaction took place only in the presence of ATP:¹⁰⁸



The effects of TPN and ATP on pigeon-liver oxaloacetic carboxylase have now been examined.¹⁰⁹ ATP causes a small inhibition of the decarboxylation of oxaloacetic acid, whilst TPN causes a marked stimulation. When the exchange between ¹⁴CO₂ and the β-carboxyl group was similarly studied, the reaction was found to be influenced in the opposite direction: the exchange was stimulated by ATP, but not by TPN. The pigeon-liver oxaloacetic carboxylase has recently been described by Ochoa *et al.*¹¹⁰ In the presence of Mn⁺⁺, the enzyme decarboxylates malic acid, and functions in the absence of inorganic phosphate and ATP. It is TPN specific.



The same enzyme catalyses the decomposition of oxaloacetic acid. By coupling with the glucose-6-phosphate dehydrogenase system, fixation of carbon dioxide takes place:



¹⁰⁵ M. Stephenson and H. A. Krebs, *Ann. Reports*, 1941, **38**, 257.

¹⁰⁶ *Currents in Biochemical Research*, 1946, 165.

¹⁰⁷ *Biochem. J.*, 1948, **42**, 598.

¹⁰⁸ *J. Biol. Chem.*, 1946, **164**, 455.

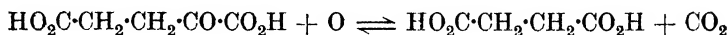
¹⁰⁹ B. Vennesland, E. A. Evans, and K. I. Altman, *ibid.*, 1947, **171**, 675.

¹¹⁰ A. H. Mehler, A. Kornberg, S. Grisolia, and S. Ochoa, *ibid.*, 1948, **174**, 961; S. Ochoa, A. H. Mehler, and A. Kornberg, *ibid.*, p. 979.

The relation of these reactions to the previously described carbon dioxide fixation in oxaloacetate, requiring ATP, is a matter for conjecture.

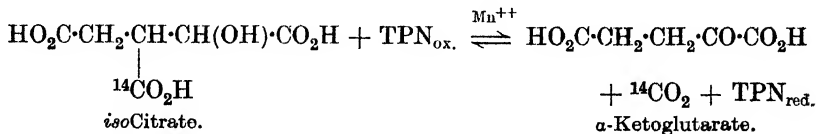
Parsley root contains an oxaloacetic carboxylase, and this reaction has also been shown to be reversible by the fixation of $^{14}\text{CO}_2$ into oxaloacetate during the decarboxylation.¹¹¹ The preparation also contained a malic dehydrogenase, and, when pyruvate and malate were incubated with $^{14}\text{CO}_2$, ^{14}C was fixed in malate. These results suggest that (analogously to animals and bacteria) the plant dicarboxylic acids are formed *via* an initial Wood-Werkman reaction. Some properties of this plant oxaloacetic carboxylase and its quantitative assay have been described recently.^{111a}

C₄ and C₁ Addition.—An important new type of heterotrophic assimilation of carbon dioxide has now been described which involves C₄ and C₁ addition.¹¹² A cell-free enzyme preparation was obtained from *E. coli* which decarboxylated α -ketoglutarate to succinate and carbon dioxide; malonate was present to inhibit the oxidation of the succinate. The system reversibly fixed $^{13}\text{CO}_2$ in the carboxyl group adjacent to the carbonyl carbon atom of ketoglutarate; fixation was increased by the addition of ATP, and it was suggested that a phosphorylated form of succinate may have been involved. This reversible oxidative decarboxylation is therefore as follows :



This observation finally completes the evidence for the complete reversal of the Krebs' tricarboxylic acid cycle. Since α -ketoglutarate could replace carbon dioxide to a greater extent than other C₄ acids, the authors suggested that normally the C₄ and C₁ addition may be of greater importance than the other known fixation reactions.

C₅ and C₁ Addition by Oxalosuccinic Carboxylase.—Since the publication of Wood's review, a detailed account has appeared of the work of Ochoa and his colleagues with the oxalosuccinic carboxylase system.¹¹³ Results similar to those of Ochoa have been obtained with isotopes.¹¹⁴ Incorporation of ^{14}C into the β -carboxyl group of *isocitric* acid took place when α -ketoglutarate and *isocitrate* were incubated with $\text{NaH}^{14}\text{CO}_3$ in the presence of an oxalosuccinic carboxylase preparation from pigeon liver.



¹¹¹ M. C. Gollub and B. Vennesland, *J. Biol. Chem.*, 1947, **169**, 233.

^{111a} B. Vennesland, M. C. Gollub, and J. F. Speck, *ibid.*, 1949, **178**, 301.

¹¹² S. J. Ajl and C. H. Werkman, *Proc. Nat. Acad. Sci.*, 1948, **34**, 491.

¹¹³ S. Ochoa, *J. Biol. Chem.*, 1948, **174**, 115, 133; S. Ochoa and E. Weisz-Tabori, *ibid.*, p. 123.

¹¹⁴ S. Grisolia and B. Vennesland, *ibid.*, 1947, **170**, 461.

A similar reaction has been studied in connection with tricarboxylic acid synthesis by carbon dioxide fixation in parsley root preparations.¹¹⁶

Carbon Dioxide Utilisation by the Animal.—Despite the relatively large output of carbon dioxide by the intact animal, it has been possible to study carbon dioxide utilisation; A. M. Delluva and D. W. Wilson gave hourly intraperitoneal injections of $\text{NaH}^{13}\text{CO}_3$ (18 hours) to a rat.¹¹⁵ ^{13}C was found in a carboxyl group of aspartate and the α -carboxyl group of glutamate. These compounds were presumably derived from amination of the primary fixation products, oxaloacetate and α -ketoglutarate. (In a study of the *in vitro* turnover of dicarboxylic amino-acids in liver slice proteins, ^{14}C from $\text{Na}_2^{14}\text{CO}_3$ was similarly incorporated entirely into these acids *via* α -ketoglutarate and oxaloacetate.) ^{13}C was also found in the amidino-carbon atom of arginine, again supporting the participation of arginine in Krebs' urea cycle.

Armstrong and his co-workers have studied the distribution of ^{14}C following incorporation from inorganic carbonates (Na , Ba , Ca).¹¹⁷ A very small fraction of ^{14}C was incorporated into the fatty acids, and to a lesser extent into the unsaturated fatty acids. The ^{14}C content of the carboxyl group of the saturated and total fatty acids was twice as great as the average of all the carbon atoms in the respective fatty acids. Absorption of ^{14}C activity from intraperitoneally implanted $\text{Ca}^{14}\text{CO}_3$ pellets was slower, but gave greater incorporation than the intraperitoneal injection of $\text{Na}_2^{14}\text{CO}_3$. ^{14}C was found in many compounds including hæmin, fatty acids, and glycerol.

In other experiments, the rate of $^{14}\text{CO}_2$ excretion following intraperitoneal administration of isotopic bicarbonate (and acetate) has been followed.¹¹⁸ The excretion reached a maximum within 10 minutes of injection, and thereafter the specific activity of respiratory CO_2 decreased exponentially for about an hour; the rate of decrease then became considerably slower.

R. B.

3. PARTITION CHROMATOGRAPHY.

Partition chromatography has now a substantial literature, which is rapidly increasing. This technique has already been applied to the separation of some 200 substances. Review articles on chromatography, including partition chromatography, have been published; ^{1, 2} R. L. M. Synge ³ and A. J. P. Martin ⁴ have written on partition chromatography, and M. Hais ⁵

¹¹⁵ J. Biol. Chem., 1946, **166**, 739.

¹¹⁶ B. Vennesland, J. Ceithaml, and M. C. Gollub, *ibid.*, 1947, **171**, 445; J. Ceithaml and B. Vennesland, *ibid.*, 1949, **178**, 133.

¹¹⁷ J. D. Schubert and W. D. Armstrong, *Science*, 1948, **108**, 286; W. D. Armstrong, J. Schubert, and A. Lindenbaum, *Fed. Proc.*, 1948, **7**, 143.

¹¹⁸ R. G. Gould, I. M. Rosenberg, M. Sinex, and A. B. Hastings, *ibid.*, p. 156.

¹ A. J. P. Martin, *Endeavour*, 1947, **6**, 21.

² T. I. Williams, *Research*, 1948, **1**, 400.

³ *Analyst*, 1946, **71**, 256.

⁴ *Ann. N.Y. Acad. Sci.*, 1948, **49**, 249.

⁵ *Chem. Listy*, 1948, **42**, 125.

and R. Consden⁶ on partition chromatography on paper (for which the name "papyrography" has been suggested;⁷ cf. "papergrams"⁸). Chromatography of amino-acids and peptides has been discussed by Martin and Synge⁹ and by E. Brand and J. T. Edsall.¹⁰ The Biochemical Society has held a symposium on partition chromatography.¹¹

Theoretical.

Principles of Chromatography.—Theories of chromatography make basic assumptions about (a) the equilibrium concentrations of solutes between the moving and the stationary parts of the chromatogram (*i.e.*, the adsorption isotherm or partition coefficient), (b) the rate of establishment of equilibrium, (c) the diffusion of the solute between moving and stationary parts, and (d) the diffusion of solute along the length of the column. They are not necessarily concerned with mechanisms responsible for the relations assumed. Thus, in general, the theory of adsorption and of partition chromatograms is the same.

No theory has yet attempted to take account of all known important factors. For instance, J. N. Wilson,¹² D. De Vault,¹³ J. Weiss,¹⁴ and E. Glueckauf¹⁵ assumed instantaneous equilibrium and no diffusion, but allowed for a non-linear adsorption isotherm. These theories have been applied chiefly to adsorption chromatograms where the adsorption isotherms are frequently strongly curved and establishment of equilibrium is rapid. Martin and Synge¹⁶ assumed a linear isotherm (constant partition coefficient), introduced the "theoretical plate" concept from distillation theory to allow for diffusion from moving to stationary parts, and neglected other diffusion. S. W. Mayer and E. R. Tompkins¹⁷ developed this theory to permit easy calculation of the concentration in the effluent. The theory has been applied to partition and ion-exchange chromatograms where the partition coefficient is practically constant. A. A. Levi¹⁸ applied De Vault's theory to a buffer-loaded partition column where so much acid had been used that appreciable changes of pH resulted and the partition coefficient was no longer constant. Caution must be used in drawing conclusions from this theory for it might be inferred that a long column possesses no advantage over a short, wide one of the same weight,¹⁸ a deduction rendered possible only because diffusion of all kinds has been neglected. H. C. Thomas¹⁹ and L. G. Sillen²⁰ have included a slow adsorption in the theory,

⁶ *Nature*, 1948, **162**, 359.

⁷ C. E. Dent, *Biochem. J.*, 1948, **43**, 169.

⁸ R. M. Tamarelli and K. Florey, *Science*, 1948, **107**, 630.

⁹ *Advances in Protein Chemistry*, 1945, **2**, 1.

¹⁰ *Ann. Rev. Biochem.*, 1947, **16**, 223.

¹¹ Proceedings of Symposium on Partition Chromatography, Biochemical Society, 1949.

¹² *J. Amer. Chem. Soc.*, 1940, **62**, 1583.

¹³ *Ibid.*, 1943, **65**, 582.

¹⁴ *J.*, 1943, 297.

¹⁵ *J.*, 1947, 1302, 1308, 1321.

¹⁶ *Biochem. J.*, 1941, **35**, 1358.

¹⁷ *J. Amer. Chem. Soc.*, 1947, **69**, 2866.

¹⁸ *Biochem. J.*, 1948, **43**, 257.

¹⁹ *Ann. N.Y. Acad. Sci.*, 1948, **49**, 161.

²⁰ *Arkiv Kemi, Min., Geol.*, 1946, **22**, A, No. 15.

as has E. Glueckauf,²¹ who in a preliminary paper²² has written an equation with terms for most of the factors mentioned above. There would appear to be little hope of any solution of this equation simple enough to be useful.

A. Tiselius²³ has given a simple theory of displacement development, and he and S. Claesson²⁴ develop a general theory of frontal analysis, instantaneous equilibrium being assumed in each case. Martin¹¹ has given an approximate theory of displacement development on buffered or acid- or base-loaded columns, using the theoretical plate method and showing the close analogy with a distillation column operating at total reflux. It can be inferred from the theory that these displacement columns have not only a high capacity, but also a high resolving power. Nothing has been published concerning the application of these columns, but wide use both in industry and in the laboratory should be possible.

Factors influencing the Partition Coefficient.—Martin¹¹ has considered the factors upon which partition coefficients depend and suggests the following rules :

(1) Let α_A be the partition coefficient of substance A and α_B that of substance B between a given pair of phases. Then, if A and B differ only in that B has a given extra group, *e.g.*, OH, CH₂, glycy, etc., the ratio α_A/α_B depends only on the extra group and on the pair of phases.

(2) As a corollary, the ratio α_A/α_B for substances A and B is unchanged by forming derivatives AX and BX, *i.e.*, $\alpha_A/\alpha_B = \alpha_{AX}/\alpha_{BX} = \alpha_{AY}/\alpha_{BY} = \dots$ etc. Thus the ease of separating two substances in a given solvent system will be unchanged whatever derivative be employed, provided that such a derivative be chosen that α does not have an inconveniently high or low value.

(3) Isomers containing the same functional groups should have identical partition coefficients.

Deviations from these rules will be largely the result of steric factors. Hence it is probable that adsorption on a solid will, in general, distinguish better between isomers than does partition between liquids.

Varieties of Partition Chromatograms.—The partition chromatogram used by Martin and Synge¹⁶ for the separation of acetylated amino-acids consisted of precipitated silica loaded with water. Various modifications have since been made to extend its use to other substances. Heilbron and his co-workers^{25, 26} added a basic substance, *e.g.*, barium carbonate, to the silica and thereby were able to retain penicillin on the columns. A frontal analysis type of chromatogram thereby resulted, which gave only partial

²¹ *J.*, 1947, 1315.

²² Discussion on New Techniques, Chemical Society, Nov. 25th, 1948.

²³ See *Advances in Protein Chemistry*, 1947, **3**, 67.

²⁴ *Arkiv Kemi, Min., Geol.*, 1946, **23**, A, No. 1.

²⁵ R. C. Elliott, I. M. Heilbron, A. H. Cook, and J. R. Catch, B.P. 558,320.

²⁶ J. R. Catch, A. H. Cook, and I. M. Heilbron, *Nature*, 1942, **150**, 633.

separation (see Tiselius²³).^{*} Levi²⁷ used a strong phosphate buffer instead of barium carbonate, obtaining the usual type of elution development, and was able to effect the first clear separation of different penicillins. The use of buffers on the chromatogram for the separation of acidic and basic substances is now well established, and various applications of it will be mentioned below. A. H. Gordon, A. J. P. Martin, and R. L. M. Synge²⁸ used two non-aqueous phases on precipitated silica in an attempt to purify gramicidin. Since then a variety of non-aqueous systems has been used.

Instead of silica, R. Consden, A. H. Gordon, and A. J. P. Martin²⁹ used filter-paper for amino-acid separations, and also introduced the use of development in two dimensions. R. R. Goodall and A. A. Levi³⁰ used paper loaded with buffer for penicillin separations. Synge³¹ used starch columns for amino-acids and peptides. Kieselguhr has been proposed,²⁵ among other substances, as an alternative to precipitated silica. It has been used with buffers for penicillin and with sulphuric acid for fatty-acid separations.³² Martin¹¹ has suggested that it could replace precipitated silica with advantage in many cases.

The partition chromatogram works conveniently within a range of partition coefficients of 1 : 1 to 1 : 100 in favour of the stationary phase. A wide extension of its use should be possible, therefore, if means could be found for making the less polar phase the stationary one. To this end, R. J. Boscott³³ has suggested the use of acetylcellulose and J. Boldingh³⁴ has used paper loaded with vulcanised rubber latex, and methanol as solvent, for the separation of esters of higher fatty acids. Martin,³⁵ by treating kieselguhr with dimethyldichlorosilane, has given it a surface not readily wettable by polar solvents; thus treated, it will satisfactorily hold the less polar of a given phase pair.

G. Haugaard and T. D. Kroner³⁶ have used simultaneous separation in a horizontal direction by ionophoresis and in a vertical direction by partition chromatography. The paper is loaded with buffer and vertical electrodes are attached near the edges of the paper. The whole is then developed as a chromatogram in the usual way.

²⁷ A. A. Levi, S. G. Terjessen, and I.C.I., B.P. 569,844; see also ref. 18.

²⁸ *Biochem. J.*, 1943, **37**, 86.

²⁹ *Ibid.*, 1944, **38**, 224.

³⁰ *Nature*, 1946, **158**, 675.

³¹ *Biochem. J.*, 1944, **38**, 285.

³² M. H. Petersen and M. J. Johnson, *J. Biol. Chem.*, 1948, **174**, 775.

³³ *Nature*, 1947, **159**, 342.

³⁴ *Experientia*, 1948, **4**, 270.

³⁵ To be published.

³⁶ *J. Amer. Chem. Soc.*, 1948, **70**, 2135.

^{*} In this type of chromatogram only the fastest-running material can be obtained pure, for some of the substance of each zone extends back to the top of the column. Thus, if the substances A, B, C, and D are run on a frontal-analysis column, zone 1 contains A, zone 2 contains A + B, zone 3 contains A + B + C, and zone 4 contains A + B + C + D, the proportions of A, B, C, and D in zone 4 being those which would be found in the stationary phase if a small volume of the latter were shaken with a large volume of the original solution in the mobile phase. If this type of column is developed with an acid, E, slower moving than D, a displacement chromatogram is established in which, finally, the zones consist of A, B, C, D, and E more or less sharply separated from each other.

Absorption.—It is not possible, in all cases, to eliminate adsorption on the carrier material, *e.g.*, silica, starch, or cellulose. In the original columns of precipitated silica,¹⁶ a small percentage of alcohol was necessary to reduce adsorption, and later various empirical methods of preparation³⁷ were advocated to obtain non-adsorptive silica. The problem of its preparation has not yet been completely solved. Kieselguhr may well prove to be less adsorptive. When buffers are used on the column, adsorption seems to cause less trouble.³⁸

When cellulose or starch is used as support, it is more difficult to decide what part is played by adsorption. True adsorption certainly occurs. S. Moore and W. H. Stein³⁹ have demonstrated adsorption of certain amino-acids on starch, which accounts, to some extent at least, for the differences in the rates as expected from partition coefficients and as measured on the columns.

Paper chromatograms have been used for inorganic separations. Linstead and his colleagues⁴⁰ question whether the governing factor is partition in this case, because "activation" of the paper with nitric acid is desirable and solvents miscible with water can be used.

R. E. Horne and A. J. Pollard⁴¹ have used paper for streptomycin separations; 3% aqueous ammonium chloride is used as solvent. It seems improbable that partition plays any part here. Perhaps the action is as follows. The cellulose is initially saturated with water which gradually dilutes to pure water the advancing front of solvent. The streptomycin is absorbed by paper from water and eluted by ammonium chloride solution. Hence it is found near the front in a region of rising ammonium chloride concentration.

There are, however, cases where it is difficult to decide whether adsorption or partition is the proper name for what occurs. Paper chromatograms may be run with solvents miscible with water;^{29, 36} these solvents, however, are usually readily salted out. It is reasonable to suppose, therefore, that the solvent within the cellulose is richer in water than the mobile phase, the organic material being "salted out" to some extent by the cellulose. A partition coefficient differing from unity is therefore to be expected between the mobile solvent and the solvent within the cellulose. One may, however, regard the phenomenon as one of absorption by the solvent-swollen cellulose.

Partition Chromatography of Large Molecules.—The limit of size of molecule that can be handled on paper, starch, or precipitated silica is not well defined. It is not to be expected that very large molecules can penetrate

³⁷ A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *Biochem. J.*, 1944, **38**, 65; F. A. Isherwood, *ibid.*, 1946, **40**, 688; G. R. Tristram, *ibid.*, p. 721; R. Harriss and A. N. Wick, *Ind. Eng. Chem. Anal.*, 1946, **18**, 276.

³⁸ V. Moyle, E. Baldwin, and R. Scarisbrick, *Biochem. J.*, 1948, **43**, 308.

³⁹ *Ann. N. Y. Acad. Sci.*, 1948, **49**, 265.

⁴⁰ T. V. Arden, F. H. Burstall, G. R. Davies, J. A. Lewis, and R. P. Linstead, *Nature*, 1948, **162**, 691.

⁴¹ *J. Bact.*, 1948, **55**, 231.

those supporting substances, although peptides containing several amino-acid residues behave satisfactorily. Adsorption may play an increasing part as molecular size increases, and the chromatograms may act simultaneously by partition for small molecules and by adsorption for large. Kieselguhr, since it holds the stationary phase essentially in droplet form, should offer no limitation to molecular size. It may well be difficult to find two phases which are immiscible but yet are both solvents for a given very large molecule.

Apparatus.

The apparatus normally used for adsorption chromatography can be used also for partition columns. Apparatus for collecting numerous fractions of the effluent has been described by Moore and Stein;^{39, 42} a photo-cell and counter mechanism rotates a test-tube rack (80 tubes) after a predetermined number of drops. S. S. Randall and A. J. P. Martin⁴³ have used a syphon with a long arm delivering to a stationary rack; the weight of liquid operates an escapement which permits the syphon to rotate. To observe the passage of zones of ionic material, they record the conductivity of the outflowing solution.

Isherwood,³⁷ unable to use an indicator on his silica column since it was loaded with sulphuric acid, allowed the effluent to run down a capillary together with an indicator solution. Equilibration was sufficiently rapid for the presence of acid in the effluent to be detected almost immediately.

B. Drake⁴⁴ has described an automatic tester, drops of effluent falling on a drum of suitably prepared paper at regular intervals.

The apparatus used by Consden, Gordon, and Martin²⁹ for paper chromatography has been modified by several workers.^{7, 45} Methods of making glass troughs have been published;⁴⁶ however, troughs of stainless steel are perhaps the most satisfactory. Boxes of metal,^{29, 45} glass,^{29, 47} and "Perspex"⁴⁸ have all been employed. Unless temperatures are very steady, for long runs in large vessels, a penthouse roof is desirable so that condensed solvents shall not drip back on to the chromatograms.

Williams and Kirby⁴⁵ allow the solvents to rise by capillarity up a suspended strip or cylinder of paper standing in a circular jar. This method requires a minimum of apparatus, but development is slower, and solvent travel is limited to the length of the paper, a disadvantage for slow spots. An advantage for fast spots is that they cannot run off, and the chromato-

⁴² *J. Biol. Chem.*, 1948, **176**, 337.

⁴³ *Biochem. J.*, Proc. 1949.

⁴⁴ *Nature*, 1947, **160**, 602.

⁴⁵ R. D. Hotchkiss, *J. Biol. Chem.*, 1948, **175**, 315; M. Macheboeuf and J. Blass, *Ann. Inst. Pasteur*, 1947, **73**, 1053; W. A. Winsten, *Science*, 1948, **107**, 605; R. J. Williams and H. Kirby, *ibid.*, p. 481; F. C. Steward, W. Stepka, and J. P. Thompson, *ibid.*, p. 451; R. R. Goodall and A. A. Levi, *Analyst*, 1947, **72**, 277; P. B. Baker, F. Dobson, and A. J. Martin, *Nature*, in the press.

⁴⁶ W. H. Longenecker, *Science*, 1948, **107**, 23; H. F. Atkinson, *Nature*, 1948, **162**, 858.

⁴⁷ Hotchkiss, *loc. cit.*, ref. 45; Winsten, *ibid*; Williams and Kirby, *ibid*.

⁴⁸ Baker, Dobson, and Martin, *Nature*, in the press.

gram can be left unattended for long periods. The resolution of the spots for the same development seems unaffected.

The use of very volatile solvents and of paper loaded with strong buffer solutions presents special problems in maintaining the atmosphere exactly saturated with respect to both phases. Goodall and Levi⁴⁵ used paper loaded with 30% potassium phosphate solution and diethyl ether as solvents for penicillin separations. They operated in a chamber with minimum free space at 0°; a wet cloth lined an inner wall to maintain a water-saturated atmosphere. This procedure may be criticised on the grounds that no equilibrium can be set up between atmosphere and strip. Baker, Dobson, and Martin⁴⁵ pumped a mixture of the two phases or of organic phase and a salt solution of the required vapour pressure continuously over cloth on the inner walls of the tank. The strips came rapidly to equilibrium and reproducible chromatograms were readily obtained. They believe this method to be of general utility for volatile solvents and for buffered paper.

Consden, Gordon, and Martin⁴⁹ and C. E. Dent⁵⁰ have described pieces of apparatus for eluting peptides spots from chromatograms and also for their subsequent hydrolysis and deamination.

D. M. P. Phillips⁵¹ has devised a graduated rubber strip for the rapid estimation of R_F values. (The R_F value is the ratio of the movement of the spot to the movement of the solvent front.²⁹)

Consden, Gordon, and Martin⁴⁹ have described a method for removing salts from amino-acid solutions before chromatography.

Methods for detecting Substances on Paper Chromatograms, and Special Methods of Identification.

Before use can be made of paper chromatograms, a method for detecting a few micrograms or less of the substances to be investigated must be available. A general reagent, revealing a large number of different substances, is the most valuable. The positions of the spots usually limit identification to a small number of possibilities, for which other means of selection should ideally be available. It is clear that determination of the R_F value alone is not as good a method of identification as is comparison of the position of the unknown with those of other substances, preferably nearly related, run simultaneously on the same chromatogram.⁵² The symbols R_g ⁵³ and R_r ⁵⁴ have been used to denote the R_F values relative to those for tetramethyl glucose and proline, respectively, in recognition of

⁴⁹ *Biochem. J.*, 1947, **41**, 590.

⁵⁰ *Lancet*, 1946, **251**, 637; *Biochem. J.*, 1947, **41**, 240; C. E. Dent and C. Rimington, *ibid.*, p. 253.

⁵¹ *Nature*, 1948, **162**, 29.

⁵² R. Consden, A. H. Gordon, A. J. P. Martin, O. Rosenheim, and R. L. M. Synge, *Biochem. J.*, 1945, **39**, 251.

⁵³ F. Brown, E. L. Hirst, L. Hough, J. K. N. Jones, and W. H. Wadman, *Nature*, 1948, **161**, 720.

⁵⁴ R. Raper and J. Shaw, *ibid.*, 1948, **162**, 999.

the fact that relative R_f values are more reliable than absolute ones. In two-dimensional chromatograms of amino-acids, the general pattern of spots leaves no doubt as to the identity of most of them; in one-dimensional strips, identification is possible only with simple mixtures. When tissue extracts or partial hydrolysates, or, in general, any ill-defined mixture is examined, many spots may require an *ad hoc* research for their identification.

For revealing amino-acids, peptides, certain amines, and amino-sugars, ninhydrin (triketointhane hydrate) still holds pride of place. Acetic acid⁵⁵ should be added if salts are present in the mixture to be analysed. Dent⁷ prefers to allow the colour to develop in a warm room, and later uses heat to reveal certain substances which react only when hot. Tables of R_f values and colours with ninhydrin have been listed.^{7, 29, 49, 50, 56}

The Pauli reagent may be used for tyrosine or di-iodotyrosine,⁷ histidine,^{7, 57} and histamine; ⁷ Ehrlich's reagent, dimethylaminobenzaldehyde, may be used for tryptophan,³¹ and the Sakaguchi reaction for arginine.^{7, 52} and streptomycin.^{41, 58} Periodic acid with Nessler's reagent may sometimes be used for serine or threonine,⁵⁷ but the reaction is rather insensitive. For sulphur-containing amino-acids, potassium iodoplatinate^{57, 59} or sodium azide and iodine⁶⁰ may be used.

Carbohydrates, methylated carbohydrates, and other reducing substances can be detected by ammoniacal silver nitrate;⁶¹ resorcinol and naphtharesorcinol⁶² give characteristic colours with carbohydrates. Acetylacetone and Ehrlich's aldehyde reagent have been used for amino-sugars,⁶³ potassium ferrieyanide for adrenaline-like substances,⁶⁴ and alkaline picrate for creatinine, and for creatine after its conversion into creatinine.^{50, 65}

Ultra-violet light reveals many substances by fluorescence or quenching of fluorescence, *e.g.*, amino-acids,^{60, 66} pigments of petal extracts,^{11, 67} flavins,⁶⁸ pterins,⁶⁹ porphyrins,¹¹ products of heated proteins,⁷⁰ carbohydrates after heating with *m*-phenylenediamine hydrochloride.⁶⁰ Ultra-

⁵⁵ R. Consden and A. H. Gordon, *Nature*, 1948, **162**, 180.

⁵⁶ R. Consden, A. H. Gordon, and A. J. P. Martin, *Biochem. J.*, 1946, **40**, 580; W. R. Middlebrook and H. Phillips, *ibid.*, 1947, **41**, 218; R. Consden, A. H. Gordon, and A. J. P. Martin, *Biochem. J.*, in the press; R. Consden, A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *Biochem. J.*, 1947, **41**, 596; R. Consden and A. H. Gordon, *Biochem. J.*, in the press (cf. *Biochem. J.*, 1948, **43**, x); J. J. Pratt and J. L. Auclair, *Science*, 1948, **108**, 213.

⁵⁷ R. Consden, A. H. Gordon, and A. J. P. Martin, *Biochem. J.*, 1946, **40**, 33.

⁵⁸ W. A. Winsten and E. Eigen, *J. Amer. Chem. Soc.*, 1948, **70**, 3333.

⁵⁹ H. M. Winegard, G. Toennies, and R. J. Block, *Science*, 1948, **108**, 506.

⁶⁰ E. Chargaff, C. Levine, and C. Green, *J. Biol. Chem.*, 1948, **175**, 67.

⁶¹ S. M. Partridge, *Nature*, 1946, **158**, 270.

⁶² W. G. C. Forsyth, *ibid.*, 1948, **161**, 239.

⁶³ D. Aminoff and W. T. J. Morgan, *ibid.*, 1948, **162**, 578.

⁶⁴ W. O. James, *ibid.*, 1948, **161**, 851.

⁶⁵ G. A. Maw, *ibid.*, 1947, **160**, 261.

⁶⁶ D. M. P. Phillips, *ibid.*, 1948, **161**, 153.

⁶⁷ E. C. Bate Smith, *ibid.*, p. 835.

⁶⁸ J. L. Crammer, *ibid.*, p. 349.

⁶⁹ P. M. Good and A. W. Johnson, *ibid.*, 1949, **163**, 31.

⁷⁰ A. R. Patton, E. G. Hill, and E. M. Foreman, *Science*, 1948, **108**, 659.

violet absorption of material washed from strips has been used for identification of nucleotides.⁷¹

Purines have been detected by precipitation of mercury and conversion of this into the sulphide; ⁷¹ and choline by precipitation of phosphomolybdate and reduction of this to the blue complex.⁶⁰

Biologically active substances have been detected by means of plates seeded with bacteria, e.g., penicillin,^{30, 72} streptomycin,^{41, 58} polymixin,⁷³ and growth-promoting substances.⁷⁴

D-Amino-acids can be destroyed on the chromatogram with D-amino-acid oxidase, which affords a method of distinguishing them from L-amino-acids.⁷⁵ α -Amino-acids have been differentiated from other substances giving colours with ninhydrin by treating the paper with copper carbonate before development of the chromatogram; ⁷⁶ α -amino-acid spots do not then appear, or appear in a different place, the copper complexes being faster running; ²⁹ other substances are unaffected.

The use of electron diffraction ^{77, 78} or, better, X-rays ⁷⁸ for the identification of dried extracts of chromatogram spots by comparison with authentic material, promises to be a powerful method. Although in many cases material from paper or solvent must be present in the washings, it has not prevented crystallisation, on which this method depends. Perhaps A. Engström and B. Lindström's X-ray method of elementary analysis could also be employed.⁷⁹

Use of Radio-isotopes.

R. M. Fink, C. E. Dent, and K. Fink ⁸⁰ detected substances containing radio-isotopes by presenting the chromatogram to a Geiger counter, or simply by laying it on a photographic plate, whereupon a radio-autograph results. The iodine isotope ¹³¹I has been given to rats and man, and radioactive materials detected and identified on paper strips;^{80, 81} mono- and di-iodo-tyrosine and thyroxine were all identified. Fink and Fink ⁸² exposed *Chlorella* to light and ¹⁴CO₂ for 4 hours, an alcohol extract was chromatographed, and fatty material, glucose, glutamic acid, glycine, alanine, arginine, valine, proline, aspartic acid, serine, threonine, and various unidentified spots were seen.

⁷¹ E. Vischer and E. Chargaff, *J. Biol. Chem.*, 1947, **168**, 781; see also Hotchkiss, ref. 45.

⁷² W. A. Winsten and A. H. Spark, *Science*, 1947, **106**, 192; see also Goodall and Levi, ref. 45.

⁷³ J. R. Catch, T. S. G. Jones, and S. Wilkinson, *Biochem. J.*, 1948, **43**, xxvii.

⁷⁴ W. A. Winsten and E. Eigen, *Proc. Soc. Exp. Biol. Med.*, 1948, **67**, 513; W. F. J. Cuthbertson and E. Lester Smith, *Biochem. J., Proc.*, 1949.

⁷⁵ T. S. G. Jones, *Biochem. J.*, 1948, **42**, LIX.

⁷⁶ H. R. Crumpler and C. E. Dent, to be published.

⁷⁷ A. Polson, V. M. Mosley, and R. W. G. Wyckoff, *Science*, 1947, **105**, 603.

⁷⁸ C. L. Christ, C. J. Burton, and M. C. Botty, *ibid.*, 1948, **108**, 91.

⁷⁹ *Experientia*, 1947, **3**, 191.

⁸⁰ *Nature*, 1947, **160**, 801.

⁸¹ K. Fink and R. M. Fink, *Science*, 1948, **108**, 358; R. J. Block, *Anal. Chem.*, 1948, **20**, 281.

⁸² R. M. Fink and K. Fink, *Science*, 1948, **107**, 253.

Production of amino-acids after short exposure to $^{14}\text{CO}_2$ during photosynthesis has been studied.⁸³ It is concluded that 3- and 4-carbon acids, but not glutamic acid, are produced *via* pyruvic and oxaloacetic acids.

With radioactive materials of high specific activity, quantities can be detected many orders less than the one microgram required for most colour reactions, and identification with authentic non-radioactive material is easily performed by mixed chromatograms, in which the coloured spot and the radio-autograph spot must correspond in all details of position and shape. The ease with which the chromatogram can reveal unknown metabolic products is noteworthy; *e.g.*, lysine labelled in the ϵ -position with ^{14}C is changed in the body into α -aminoadipic acid.⁸⁴ The turnover of labelled leucine in a liver peptide has been studied.⁸⁵

p-Iodophenylsulphonyl derivatives of amino-acids, containing ^{131}I , have been separated on paper, and quantitative analysis is possible by using a Geiger counter⁸⁶; ^{35}S could also be used.

The urine of rats fed with methionine labelled with ^{35}S has been examined by paper chromatography;⁸ the sulphur in the SO_4^{--} peak was highly radioactive. When benzene was injected at the same time as the methionine was given, radio-sulphur appeared mainly in the ethereal sulphate fraction, and if bromobenzene and methionine were fed together, radio-activity was divided between the SO_4^{--} peak and another due to mercapturic acid.

Separations effected by Silica Columns.

Acetamido-acids.—The partition chromatogram was introduced by Martin and Synge¹⁶ in 1941 for the separation of acetamido-acids, precipitated silica supporting an indicator solution being used, together with chloroform and a little butanol as mobile phase. Various indicators have been used.⁸⁷ The method was developed by Gordon, Martin, and Synge for acetamido-acids^{28, 37, 87} and for acetylpeptides.⁸⁸ Tristram³⁷ has made the most extensive analyses of various proteins; the method gives quantitative results for phenylalanine, leucine, *isoleucine*, valine, proline, alanine, and tyrosine. Methionine is subject to great error, probably because of oxidation.^{7, 42} The proportion of leucine to *isoleucine* has been determined by infra-red absorption.⁸⁹ Other acids may be determined in special cases.^{28, 87, 90}

⁸³ W. Stepka, A. A. Benson, and M. Calvin, *Science*, 1948, **108**, 304.

⁸⁴ H. Borsook, C. L. Deasy, A. J. Haagen Smit, G. Keighley, and P. H. Lowy, *J. Biol. Chem.*, 1948, **173**, 423; **176**, 1383.

⁸⁵ *Idem, ibid.*, **174**, 1041.

⁸⁶ A. S. Keston, S. Udenfriend, and M. Levi, *J. Amer. Chem. Soc.*, 1947, **69**, 3151.

⁸⁷ A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *Biochem. J.*, 1943, **37**, 79, 313; H. F. Liddell and H. N. Rydon, *ibid.*, 1944, **38**, 68.

⁸⁸ A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *ibid.*, 1943, **37**, 92.

⁸⁹ S. E. Darmon, G. B. B. M. Sutherland, and G. R. Tristram, *ibid.*, 1948, **42**, 508.

⁹⁰ A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *ibid.*, 1943, **37**, 538; S. Blackburn, R. Consden, and H. Phillips, *ibid.*, 1944, **38**, 25; R. L. M. Synge, *ibid.*, 1945, **39**, 363.

Dinitrophenyl Amino-acids.—F. Sanger⁹¹ and R. R. Porter and Sanger,⁹² using a variety of solvents, have separated dinitrophenyl amino-acids on silica columns. All the common dinitrophenyl amino-acids can be separated. Adsorption plays a significant part in the separations. The stability of these substances to acid hydrolysis makes possible the study of free amino-groups in proteins and peptides. Insulin and gramicidin S⁹¹ and hæmoglobins⁹² have been so studied, and also peptides liberated from insulin by oxidation.⁹³

Fatty Acids.—L. L. Ramsey and W. I. Patterson⁹⁴ and S. R. Elsdén⁹⁵ separated lower fatty acids (up to C₄) on precipitated silica with water and chloroform. Ramsey and Patterson,⁹⁶ using methylisooctane, and Moyle, Baldwin, and Scarisbrick,⁹⁸ using chloroform–butanol mixtures and buffer solutions on precipitated silica, have separated acids up to C₈. Peterson and Johnson³² used concentrated sulphuric acid on kieselguhr with benzene, and separated acids up to C₁₀. Good accuracy is claimed for all these methods.

G. Howard and A. J. P. Martin⁹⁷ have used silane-treated kieselguhr to make a column loaded with hexane, and aqueous methanol as mobile phase, for the separation of long-chain fatty acids.

Other Organic Acids.—Isherwood³⁷ separated fruit acids quantitatively on a precipitated silica column loaded with 0.5N-sulphuric acid, using chloroform–butanol mixtures as mobile phase. The method has been used to determine fumarate in animal tissues.⁹⁸ Glutamic acid can be determined after conversion into pyrrolidonecarboxylic acid.⁹⁹

Methylated Sugars.—Di-, tri-, and tetra-methyl glucose have been separated quantitatively by D. J. Bell¹ on a silica column loaded with water, chloroform–butanol being used as the mobile phase.

Penicillin.—Penicillin was studied on silica columns with added solid bases by Catch, Cook, and Heilbron;²⁶ Levi^{27, 2} used phosphate buffer as the stationary phase. The method has been widely used with both precipitated silica and kieselguhr as support, and with ether, chloroform, and various esters as mobile phase, but very little of this work has been published. The most convincing separation yet published is that by H. Fischback, T. E. Eble, and M. Mundell,³ who show almost complete separation of K, dihydro-F, F, and G penicillins. No quantitative method on these lines has been described.

Miscellaneous Substances.—L. L. Ramsey and W. I. Patterson⁴ have

⁹¹ *Biochem. J.*, 1945, **39**, 507; 1946, **40**, 261.

⁹² *Ibid.*, 1948, **42**, 287.

⁹³ F. Sanger, *Nature*, 1948, **162**, 491.

⁹⁴ *J. Assoc. Off. Agr. Chem.*, 1945, **28**, 644.

⁹⁵ S. R. Elsdén, *Biochem. J.*, 1946, **40**, 252; *J. Exp. Biol.*, 1946, **22**, 51; S. R. Elsdén, M. W. S. Hitchcock, R. A. Marshall, and A. T. Phillipson, *ibid.*, p. 191.

⁹⁶ *J. Assoc. Off. Agr. Chem.*, 1948, **31**, 139.

⁹⁷ Unpublished.

⁹⁸ L. M. Marshall, J. M. Orten, and A. H. Smith, *Science*, 1948, **108**, 92.

⁹⁹ W. E. Hanby and H. N. Rydon, *Biochem. J.*, 1946, **40**, 297.

¹ D. J. Bell, *J.*, 1944, 473.

² W. R. Boon, C. T. Calam, H. Gudgeon, and A. A. Levi, *Biochem. J.*, 1948, **43**, 262.

³ *J. Amer. Pharm. Assoc.*, 1947, **36**, 2. ⁴ *J. Assoc. Off. Agr. Chem.*, 1946, **29**, 337.

separated α -, β -, γ -, and δ -isomers and two other substances from commercial hexachlorocyclohexane; precipitated silica holding nitromethane and *n*-hexane as mobile phase were used. A quantitative method for the γ -isomer has been based on this.⁵ W. C. Evans and M. W. Partridge have quantitatively separated various solanaceous alkaloids on kieselguhr columns loaded with phosphate buffers, with ether as mobile phase.⁶ The anti-pernicious anæmia substance has been separated on various columns, including silica and starch.⁷

Separations effected by Paper Chromatograms.

Amino-acids and Peptides.—The technique of Consden, Gordon, and Martin²⁹ for amino-acid separation has been adopted with little modification. Dent⁷ uses a collidine-lutidine mixture in place of *s*-collidine, and uses it before phenol, in his two-dimensional chromatograms. Other solvents have been employed.⁸

Methods for the identification of simple peptides separated by paper chromatography have been worked out by Dent⁵⁰ and by Consden, Gordon, and Martin.⁴⁹ Most peptides containing only a few amino-acid residues run as satisfactorily on the chromatogram as do amino-acids. Basic peptides are apt to form streaks and, for these, butanol-acetic acid mixtures are valuable.^{11, 9} The number of possible peptides is so large that position alone forms a poor clue to identity; they have to be extracted and hydrolysed, and the amino-acids identified on further chromatograms. Treatment with nitrous fumes before hydrolysis distinguishes the residue carrying the free amino-group. Dinitrophenyl derivatives of amino-acids and peptides may be run on paper, and these serve also to identify the free amino-group.¹⁰

Amino-acids have been identified in potato^{11a} and other plant tissues,^{12, 13} anthers,¹³ pollen,¹⁴ insects' hæmolymph,^{54, 13} nuclear proteins,¹⁵ viruses,¹⁶ bacteria,¹⁷ hypertensin,⁸ medullated hairs,¹⁸ alkali-treated wool,¹⁹ trypsin and trypsin inhibitor,²⁰ and pathological urine.⁵⁰ Methionine *SS*-dioxide and

⁵ O. T. Aepli, P. A. Munter, and J. F. Gall, *Anal. Chem.*, 1948, **20**, 610.

⁶ *Quart. J. Pharm. Pharmacol.*, 1948, **21**, 126.

⁷ E. Lester Smith, *Nature*, 1948, **161**, 638; E. Lester Smith and L. F. J. Parker, *Biochem. J.*, 1948, **43**, viii.

⁸ P. Edman, *Arkiv Kemi, Min., Geol.*, 1945, **22**, A, No. 3.

⁹ T. S. G. Jones, *Biochem. J.*, 1948, **42**, LII; **43**, xxvii.

¹⁰ D. M. P. Phillips and J. M. L. Stephen, *Nature*, 1948, **162**, 152.

^{11a} C. E. Dent, W. Stepka, and F. C. Steward, *ibid.*, 1947, **160**, 682.

¹² A. Allsopp, *ibid.*, 1948, **161**, 833.

¹³ L. F. La Cour and R. Drew, *ibid.*, 1947, **159**, 307.

¹⁴ J. L. Auclair and C. A. Jamieson, *Science*, 1948, **108**, 357.

¹⁵ J. N. Davidson and R. A. Lawrie, *Biochem. J.*, 1948, **43**, xxix.

¹⁶ R. Markham, R. E. F. Mathews, and K. M. Smith, *Nature*, 1948, **162**, 88; A. Polson and R. W. G. Wyckoff, *Science*, 1948, **108**, 501.

¹⁷ A. Polson, *Nature*, 1948, **161**, 351; C. E. Work, VIIIth Cong. de Soc. de Chim. biol., Paris, 1948.

¹⁸ S. Blackburn, *Biochem. J.*, 1948, **43**, 114.

¹⁹ R. Cockburn, B. Drucker, and H. Lindley, *ibid.*, p. 438.

²⁰ E. Work, *ibid.*, 1948, **42**, xlix.

methionine *S*-oxide have been demonstrated in oxidised casein,⁵⁰ sulphur-containing amino-acids derived from cystine in chemically treated wool,⁵⁶ and α -amino- ϵ -hydroxyhexoic acid in deaminated casein.²¹ Casein and beef were shown to be absorbed principally as free amino-acids during digestion.²² Alanine was found during the bacterial breakdown of tryptophan.⁸⁸ Norleucine was shown to be absent from spinal cord,⁵² methionine from Bence Jones protein,²³ and hydroxylysine²⁴ from a leaf protein. Amino-acids were shown to be destroyed in heated soy globulin.⁷⁰ α -Aminobutyric acid has been found in plant¹¹ and animal extracts,⁷ γ -aminobutyric acid in potatoes,¹¹ taurine in blood,⁷ methylhistidine in dog's urine,⁷ ethanolamine-phosphoric acid and hydroxylysine-phosphoric acid in beef.²⁵

Partition chromatography has been used to control fractionation by other methods.²⁶

Polymixin⁹ has been shown to be a family of peptides, having in common threonine, α -diaminobutyric acid,⁷⁵ leucine, or phenylalanine and a fatty acid. Peptides have been distinguished in partly hydrolysed wool²⁷ and insulin⁹³ and in pathological urine.⁵⁰

The structure of gramicidin S has been examined; it was shown to be a cyclic penta- or deca-peptide containing equimolar amounts of valine, ornithine, leucine, phenylalanine, and proline.²⁸ From a partial hydrolysate, valylornithine, ornithyl-leucine, leucylphenylalanine, phenylalanyl-proline and, with less certainty, valylornithyl-leucine and phenylalanyl-prolylvaline were identified on two-dimensional chromatograms. Some of these peptides were found also when using Sanger's technique (dinitrophenyl derivatives) on a partial hydrolysate fractionated by ionophoresis. The sequence valine-ornithine-leucine-phenylalanine-proline may occur in a *cyclopentapeptide* or twice in a *cyclodecapeptide*.²⁹

Hypertensin⁸ and peptides from liver extracts,^{85, 30} although they seem to contain several amino-acids, run as fairly satisfactory spots on paper chromatograms.

Quantitative Analysis of Amino-acids.

Moore and Stein^{39, 42} have made a thorough study of the starch column and can separate many of the amino-acids by its use. Removal of metals

²¹ R. Gingras, E. Page, and R. Gaudry, *Rev. Can. Biol.*, 1947, **6**, 801.

^{21a} C. E. Dent and J. R. Schilling, *Biochem. J.*, 1948, **42**, xxix.

²² E. A. Dawes, J. Dawson, and F. C. Happold, *ibid.*, 1947, **41**, 426.

²³ C. E. Dent, *Biochem. J.*, Proc., 1949.

²⁴ J. W. H. Lugg and R. A. Weller, *ibid.*, 1948, **42**, 408.

²⁵ A. H. Gordon, *Nature*, 1948, **162**, 778.

²⁶ R. L. M. Syngé, *Biochem. J.*, 1948, **42**, 99; E. V. McCollum and A. A. Rider, *Science*, 1948, **108**, 11; T. H. Farmer, *Sci. J. Roy. Coll. Sci.*, 1947, **17**, 27; J. D. Gregory and L. C. Craig, *J. Biol. Chem.*, 1948, **172**, 839.

²⁷ A. J. P. Martin, Symposium on Fibrous Proteins, Soc. Dyers & Colourists, 1946, 1; see also Consden, Gordon, and Martin, ref. 56; Consden and Gordon, ref. 56.

²⁸ See Syngé, ref. 90; Sanger, *loc. cit.*, 1946, ref. 91.

²⁹ Consden, Gordon, Martin, and Syngé, ref. 56.

³⁰ G. H. Tishkoff, A. Zaffaroni, and H. Tesluk, *J. Biol. Chem.*, 1948, **175**, 857.

by treatment of the column with 8-hydroxyquinoline is one condition of success; great care in packing the column appears to be another. They have also investigated the ninhydrin reaction and found conditions for using it as an accurate colorimetric method.³¹ In their second paper they describe in detail the determination of phenylalanine, leucine, *isoleucine*, methionine, tyrosine, and valine. Butanol-benzyl alcohol is the mobile phase, which must include 0.5% of thiodiglycol to prevent oxidation of the methionine. Their method appears to give results as accurate as those attainable by any other, but is somewhat laborious; it has been applied to a number of proteins.

Polson, Mosley, and Wyckoff⁷⁷ have extracted the coloured ninhydrin spot with acetone from two-dimensional paper chromatograms and measured the density of colour. L. Naftalin³² completes colour development by heating with further ninhydrin after extraction. R. J. Block³³ separates neutral, acid, and basic fractions with ion-exchange resins, and after chromatography, measures the density of the spots directly on the paper. R. B. Fisher, D. S. Parsons, and G. A. Morrison³⁴ report a quantitative method for amino-acids and carbohydrates based on measurement of the spot areas on a reflex photograph of the chromatogram; the photographs have increased contrast.

A. J. Woiwod³⁵ forms the copper complex of amino-acids from the extracted chromatogram and estimates colorimetrically; Jones⁷⁵ and A. J. P. Martin and R. Mittelman³⁶ determine the copper complex polarographically. The last is the only method yet published in detail, and it is suitable only for simple mixtures. Further details and experience must be awaited before the usefulness of these methods can be assessed. Some of them seem too good to be true!

A. Polson,³⁷ by a simple visual comparison of a series of dilutions of unknown and control mixtures on one- or two-dimensional chromatograms, determines all the common amino-acids quantitatively. Results for replicate runs, and comparison with microbiological assay of *E. coli* hydrolysates, are given. The results appear surprisingly good, differences exceeding 10% being exceptional.

An ingenious method, "retention analysis," has been described by T. Wieland and E. Fischer.³⁸ A solution of copper acetate in tetrahydrofuran is allowed to flow in the chromatogram at right angles to the direction of development, as in making a two-dimensional chromatogram. The copper complex of the amino-acid which is formed moves only slowly or not at all. The solvent front is denuded of copper locally and a V-shaped indentation is formed in the copper acetate front. Since the copper acetate

³¹ *J. Biol. Chem.*, 1948, **176**, 367.

³² *Nature*, 1948, **161**, 763; see also Proceedings of Symposium on Partition Chromatography, Biochemical Society, 1949.

³³ *Science*, 1948, **108**, 608.

³⁴ *Nature*, 1948, **161**, 764.

³⁵ *Ibid.*, p. 169.

³⁶ *Biochem. J.*, 1948, **43**, 353.

³⁷ *Biochimica et Biophysica Acta*, 1948, **2**, 575.

³⁸ *Naturwiss.*, 1948, **35**, 29; T. Wieland, *Angew. Chem.*, 1948, **A**, **60**, 313.

solution is of constant composition the area of the V-shaped indentation is a measure of the amount of copper precipitated, and hence of the amino-acid present in the chromatogram spot. Finally, the copper front is rendered easily visible by treatment of the paper with dithio-oxamide (rubeanic acid, $\text{NH}_2\cdot\text{CS}\cdot\text{CS}\cdot\text{NH}_2$), in acetone, and the area of the indentation is traced on transparent paper and measured with a planimeter. The results on a few synthetic mixtures show errors not exceeding 4%. The principle of this method is obviously capable of application to a wide range of substances. So far, its use is described only on one-dimensional chromatograms and after the acid, basic, and neutral amino-acids have been separated by ionophoresis.

Carbohydrates.

Partridge^{61, 39} was able to separate practically all the common carbohydrates from each other by using essentially the same conditions and solvents as have been used for amino-acids but with addition of the use of butanol-acetic acid mixtures. Ammoniacal silver was used for detection. The occurrence of many different carbohydrates together is rare, so that two-dimensional chromatograms are not often needed. Colour reactions have been developed by Forsyth.⁶² Jones and his colleagues^{53, 40} separated methylated sugars. They have also extracted sugars from the chromatogram and performed quantitative determinations, using the Somogyi reagent or determining formaldehyde after oxidation. J. R. Hawthorne⁴¹ has estimated extracted sugars quantitatively by measuring excess of reagent after oxidation by hypiodous acid.

These methods have been used for investigation of the blood group A substance,^{63, 39, 42} shiga polysaccharide,³⁹ structure of starch,⁴³ cellulose of marine algæ,⁴⁴ and the carbohydrate metabolism of micro-organisms.⁴⁵

Nucleotides and Related Substances.

Vischer and Chargaff⁷¹ have separated guanine, adenine, and xanthine, uracil and thymine by using a quinoline-collidine mixture. Extracted material was identified by its ultra-violet absorption spectrum. Hotchkiss,⁴⁵ using butanol with ammonia, separated cytosine, uracil, adenine and thymine, cytidine, guanosine, adenosine and thymidine. The chromatograms were cut across into narrow strips, each of which was extracted and the extract examined for ultra-violet absorption. The method carried an error of perhaps 10%, or less if binary mixtures were analysed.

³⁹ *Biochem. J.*, 1948, **42**, 238 (with addendum by R. G. Westall); *ibid.*, p. 251.

⁴⁰ A. E. Flood, E. L. Hirst, and J. K. N. Jones, *Nature*, 1947, **160**, 86; T. G. Halsall, E. L. Hirst, J. K. N. Jones, and A. Roudier, *ibid.*, p. 899; L. Hough, J. K. N. Jones, and W. H. Wadman, *ibid.*, 1948, **162**, 448.

⁴¹ *Ibid.*, 1947, **160**, 714.

⁴² D. Aminoff, W. T. J. Morgan, and W. M. Watkins, *Biochem. J.*, 1948, **43**, xxxvi.

⁴³ Halsall, Hirst, Jones, and Roudier, ref. 40.

⁴⁴ E. G. V. Percival and A. G. Ross, *Nature*, 1948, **162**, 805.

⁴⁵ W. G. C. Forsyth and D. M. Webley, *ibid.*, p. 150.

Crammer⁶⁸ has separated riboflavin phosphate, flavin adenine dinucleotide, and riboflavin from tissues. He and Good and Johnson⁶⁹ have separated pterins with butanol-acetic acid mixtures. Flavin production by diphtheria has also been studied.⁴⁶

P. Reichard⁴⁷ has used starch columns with butanol for separation of ribonucleosides.

Separation of Miscellaneous Substances.

Separation of penicillin on buffer-loaded paper is reported by Goodall and Levi³⁰ and by Winsten and Spark.⁷² The penicillin was detected by laying the chromatograms on agar seeded with a sensitive organism. Goodall and Levi⁴⁵ have developed the method quantitatively. Baker, Dobson, and Martin⁴⁵ have chromatographed on buffered papers the hydroxamic acids derived from penicillin. *iso*Propyl ether-*iso*propyl alcohol mixtures were used as mobile phase. The spots were revealed by their colour with ferric chloride and could be extracted and determined colorimetrically. The errors are probably smaller than in the biological method, which may have advantages, however, in the detection of small percentages of other penicillins in one nearly pure penicillin.

Winsten and Eigen⁵⁸ have studied streptomycin on paper, using 2% toluenesulphonic acid as stationary phase and butanol with 2% of piperidine as mobile phase. At least five antibiotics have been demonstrated in crude samples of streptomycin.

J. W. H. Lugg and B. T. Overell⁴⁸ separated various organic acids by using butanol-acetic acid mixtures and detected them by spraying with an indicator after drying the chromatogram. The behaviour of creatine and creatinine has been studied by G. A. Maw.^{65, 49} Two-dimensional chromatograms of several substances, not amino-acids, but giving colours with ninhydrin, are described by Dent.⁷

Boldingh³⁴ has separated the ethyl esters of long-chain fatty acids on paper laden with 30% of vulcanised rubber latex, using methanol as mobile phase.

Anthocyanins and related substances in petals have been extensively studied by Bate Smith.^{67, 50} Butanol-acetic acid is a favoured solvent. Chromatographic and fluorescent behaviour and colour reactions have served to distinguish a very large number of substances. The different substances produced by different strains of the same species are easily followed, and the methods should be of value in genetical studies.

James⁶⁴ has separated adrenalin, noradrenalin, methyladrenalin, and related substances by using phenol.

Four biologically active fractions have been separated from liver extracts and detected on agar seeded with *Lactobacillus lactis*.⁵¹

⁴⁶ A. J. Woiwod and F. V. Linggood, *Nature*, 1948, **162**, 219.

⁴⁷ *Ibid.*, p. 662. ⁴⁸ *Ibid.*, 1947, **160**, 87. ⁴⁹ *Biochem. J.*, 1948, **43**, 142.

⁵⁰ E. C. Bate Smith, to be published; see also Proceedings of Symposium, etc., ref. 11.

⁵¹ Cuthbertson and Lester Smith, ref. 74.

Inorganic Separations.

Partridge and Westall³⁹ and Consden and Gordon⁵⁵ noticed the separation, during phenol and collidine runs, of ions of the common inorganic salts.

Linstead and his colleagues^{40, 52} have studied the behaviour of many metals and can separate on paper strips, or packed columns of cellulose, the members of the following groups : (Ca, Ba, Sr), (Ni, Mn, Co, Cu, Fe), (Bi, Cd, Cu, Pb, Hg), (Al, Ga, In, Zn), (As, Sb, Sn), and the noble metals. M. Lederer⁵³ has also separated the last. A variety of solvents has been used, and concentrated hydrochloric or nitric acid or other complexing reagents are present to make the metals soluble in the rather fatty mobile phases. After development and separation, the metals may be determined by conventional means.

A. J. P. M.

4. THE CHEMISTRY OF INSULIN.

Since the isolation of insulin in a crystalline form by J. J. Abel¹ in 1926, it has become increasingly clear that the active principle is itself a protein, composed only of amino-acids. It has all the properties usually associated with proteins, and many attempts to discover a non-protein prosthetic group have failed. The only non-amino-acid component of crystalline insulin is a small amount of loosely bound zinc, which is necessary for the formation of crystals. The chemistry of insulin is thus part of the wider problem of protein chemistry and it is the methods of protein chemistry that have been most effective in the study of its structure. This review therefore deals with the study of insulin as a protein, and attempts to illustrate the methods now available for investigating proteins and to summarise our present knowledge of its structure. No attempt is made to deal with the physiological aspects of insulin action and emphasis is laid only upon the more recent developments. A number of reviews of the older literature^{2, 3, 4, 5} and on the physiological aspects^{2, 6, 7, 8, 9} are available.

⁵² R. P. Linstead, Discussion on New Techniques, Chemical Society, Nov. 25th, 1948; F. H. Burstall, G. R. Davies, R. P. Linstead, and R. A. Wells, *Nature*, 1949, **163**, 64.

⁶³ *Ibid.*, 1948, **162**, 776.

¹ *Proc. Nat. Acad. Sci.*, 1926, **12**, 132.

² H. F. Jensen, "Insulin; Its Chemistry and Physiology," New York, 1938.

³ V. du Vigneaud, *J. Washington Acad. Sci.*, 1937, **27**, 365; *Cold Spring Harbor Symp. quant. Biol.*, 1938, **6**, 275.

⁴ A. White, *ibid.*, 1938, **6**, 262.

⁵ H. Fraenkel-Conrat, *Ann. Rev. Biochem.*, 1943, **12**, 276.

⁶ D. W. Hill and F. O. Howitt, "Insulin; Its Production, Purification and Physiological Action," Hutchinson's Scientific and Technical Publications, 1936.

⁷ S. Soskin and R. Levine, "Carbohydrate Metabolism," University of Chicago Press, 1946.

⁸ J. P. Bouckaert and C. de Duve, *Physiol. Rev.*, 1947, **27**, 39.

⁹ T. F. Gallagher, *Ann. Rev. Biochem.*, 1948, **17**, 353.

The Molecular Weight of Insulin.—Using the ultracentrifuge, G. L. Miller and K. J. I. Andersson¹⁰ found a molecular weight of 46,000 for insulin. Recent determinations in the ultracentrifuge¹¹ and by osmotic pressure¹² confirm this in giving a value of 47,000—48,000 for 0.5—1.0% solutions of insulin at pH 7, though the molecule dissociates in acid or alkaline solutions.^{13, 14} In contrast to these values D. Crowfoot¹⁵ calculated the size of the unit cell from X-ray measurements and deduced a molecular weight of 36,000. This unit cell possesses trigonal symmetry, indicating that it is built up of three identical or almost identical units of molecular weight 12,000. The simplest explanation¹⁴ of these results is that the real molecular weight of insulin is in fact 12,000, and that in solution four such units are loosely bound to form molecules of molecular weight 48,000, whereas in the crystals three such units are combined in the unit cell. Confirmation for this theory was obtained by Gutfreund,¹⁴ who showed that on dilution and in acid solutions the molecular weight is lowered, indicating dissociation, and by combining the two effects he was able to demonstrate a minimum molecular weight of about 12,000. This figure was also found by A. C. Chibnall¹⁶ to be the lowest value for the molecular weight that would fit all the figures for the amino-acid analyses.

Probably the first to put forward a value of this order for the molecular weight of insulin was F. Lindner,¹⁷ who isolated a compound of insulin with a basic protein from fresh pancreas. This complex, which he considered to be the genuine depot insulin or “nativinsulin,” had a molecular weight of 15,000—20,000, indicating that it was built up of one molecule of insulin of molecular weight about 10,000 combined with a basic protein. He also showed that protamine-zinc-insulin, the complex formed by combination of protamine with insulin, had a lower molecular weight than insulin.

Using the ultracentrifuge in a study of the effects of detergents on insulin, G. L. Miller and K. J. L. Andersson¹⁸ found that when insulin was dissolved in a 2% solution of the detergent, “Dupanol”, it formed aggregates with the “Dupanol” which had the molecular weight 27,600. The micellar weight of the dupanol was 12,500, suggesting a molecular weight of the order of 15,000 for the insulin present in these aggregates.

There is thus considerable evidence that the real molecular weight of insulin is 12,000, and that in relatively concentrated neutral solutions aggregates of 4 molecules of insulin are formed, which dissociate on dilution and at extreme pH values. On crystallisation 3 molecules form the unit

¹⁰ *J. Biol. Chem.*, 1942, **144**, 459.

¹¹ H. Gutfreund and A. G. Ogston, *Biochem J.*, 1946, **40**, 432.

¹² H. Gutfreund, *ibid.*, 1948, **42**, 156.

¹³ B. Sjogren and T. Svedberg, *J. Amer. Chem. Soc.*, 1931, **53**, 2657.

¹⁴ H. Gutfreund, *Biochem. J.*, 1948, **42**, 544.

¹⁵ *Proc. Roy. Soc., A*, 1938, **164**, 580.

¹⁶ *J. Soc. Leather Trades' Chem.*, 1946, **30**, 1.

¹⁷ *Med. u. Chem.*, 1942, **4**, 248; *Chem. Abs.*, 1945, **39**, 1731.

¹⁸ *J. Biol. Chem.*, 1942, **144**, 475.

cell, and in the presence of a detergent or basic protein, complexes are formed containing one molecule of insulin. These changes are summarised diagrammatically in Fig. 1.

The "Heat Precipitation" of Insulin.—When insulin is heated in weakly acid solutions it forms an insoluble precipitate which is physiologically inactive.^{19, 20, 21} This "heat precipitate" can, however, be re-activated by treatment with dilute alkali to give a regenerated product which appears to be identical with the original insulin.²² The ability to form a "heat precipitate" appears to be a unique property of insulin, and is dependent on the intact structure of the molecule.

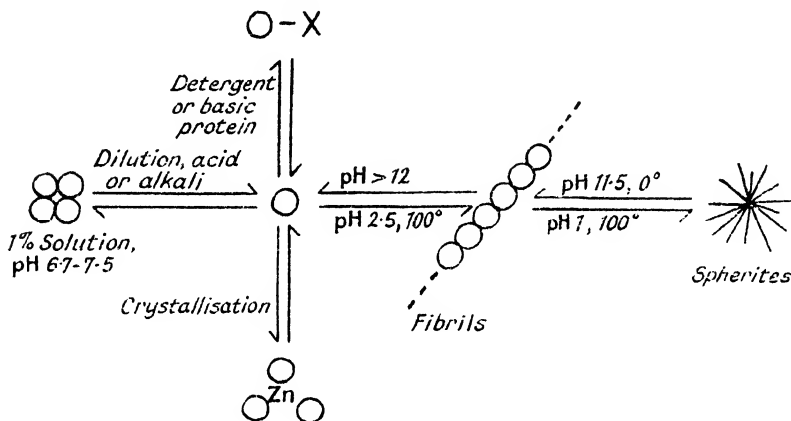


FIG. 1.

Recently Waugh^{22, 23, 24} has studied this reaction in some detail, and has demonstrated that it takes place in two stages. The first stage is characterised by the formation of fibrils, and the second by the aggregation of these fibrils to form spherites. These spherites are the visible "heat precipitate." By heating insulin at pH 2.5 a thixotropic gel is produced which consists of fibrils having lengths of about 20,000 Å. and widths of about 150 Å. In stronger acid (0.1N-HCl) these fibrils aggregate to form spherites in which the fibrils are statistically oriented radially. The nature of the spherites produced depends on the lengths of the fibrils. Thus short fibrils will form compact, well-oriented spherites, whereas long fibrils form badly oriented spherites or may only form a gel.

Waugh concludes that the fibrils are actually formed by the endwise linkage of the globular units of insulin, and that the molecule is not unfolded

¹⁹ V. du Vigneaud, E. M. K. Goiling, and C. A. Eddy, *J. Pharm. Exp. Ther.*, 1928, **33**, 497.

²⁰ T. D. Gerlogh and R. W. Bates, *ibid.*, 1932, **45**, 19.

²¹ V. du Vigneaud, R. H. Sifferd, and R. R. Sealock, *J. Biol. Chem.*, 1933, **102**, 521.

²² D. F. Waugh, *J. Amer. Chem. Soc.*, 1948, **70**, 1850.

²³ I. Langmuir and D. F. Waugh, *ibid.*, 1940, **62**, 2771.

²⁴ D. F. Waugh, *ibid.*, 1946, **68**, 247.

in any way. This reaction is thus distinguished from the more usual types of denaturation in which globular proteins appear to unfold in a random manner before aggregation. In fact insulin is generally regarded as being incapable of denaturation, until the -S-S- bridges, which are presumed to hold together the relatively short chains, are broken.²⁵ Since heat precipitation takes place in acid solution, where insulin is largely dissociated into molecules of molecular weight 12,000, it would seem probable that it is the endwise linkage of these units rather than those of molecular weight 48,000 which forms the fibril. The various changes involved in the "heat precipitation" reactions are summarised in Fig. 1.

Amino-acid Composition of Insulin.—As already indicated, insulin is built up of amino-acids. The estimation of the amount of the different amino-acids present is thus of fundamental importance and the first step in investigating the chemical structure of the molecule. Insulin has been shown to contain all the amino-acids that are usually found in proteins except tryptophan, methionine, and the rarer amino-acids hydroxyproline and hydroxylysine.

Compared with other proteins insulin has an unusually high sulphur content. It was early realised that most of this was present in the form of cystine residues,²⁶ but there was considerable doubt as to whether all the sulphur was due to cystine or whether there was some other sulphur-containing amino-acid present in insulin. This was suspected since, under the usual conditions of estimation by the specific Sullivan method, all the sulphur could not be accounted for as cystine. The nature of the sulphur present was of particular interest since it appeared that the physiological activity depended on maintaining the state of linkage of the sulphur intact, and it was suspected that a new sulphur compound might be concerned in the "active centre" of insulin. However, thorough searches especially by du Vigneaud and his collaborators³ have not yet revealed any sulphur-containing residue other than cystine. In fact G. L. Miller and V. du Vigneaud²⁷ were able to show that all the sulphur could be accounted for as cystine by the Sullivan procedure if the hydrolysis were carried out in a mixture of hydrochloric acid and formic acid instead of the conventional 20% hydrochloric acid, which caused incomplete hydrolysis and the destruction of certain labile cystine residues.

B. Kassell and E. Brand²⁸ showed that a small amount of volatile iodide was produced on treatment with hydriodic acid by the Baernstein procedure, suggesting the presence of methionine. However, V. du Vigneaud, G. L. Miller, and C. J. Rodden,²⁹ using the more specific homocysteine thiolactone method for estimating methionine, were able to show that it was absent, and found that the volatile iodide was not methyl iodide,

²⁵ K. M. Rudall, "Symposium on Fibrous Proteins," The Society of Dyers & Colourists, 1946, 15.

²⁶ V. du Vigneaud, H. Jensen, and O. Wintersteiner, *J. Pharm. Exp. Ther.*, 1928, **32**, 367.

²⁷ *J. Biol. Chem.*, 1937, **113**, 101.

²⁸ *Proc. Soc. Exp. Biol. Med.*, 1936, **35**, 444.

²⁹ *J. Biol. Chem.*, 1939, **131**, 631.

and that the amount produced was greatly reduced by hydrolysis of the protein, suggesting that it was due to certain labile groupings, the nature of which is still unknown.

Methods for the analysis of the different amino-acids have now reached a stage of development where it is possible to determine all the naturally-occurring amino-acids with considerable accuracy. Probably the most thorough and accurate analyses of insulin are those carried out by G. R. Tristram,³⁰ H. T. Macpherson,³¹ and M. W. Rees³² in Chibnall's laboratory. These workers have used the most reliable methods available, and where possible have used different methods for estimating the same amino-acids, and have carried out careful control analyses with amino-acid mixtures. A preliminary, though thorough, analysis has been carried out by E. Brand³³ and his collaborators, who have made extensive use of microbiological methods. As these were not used by the former workers they constitute a valuable check, especially for the monoamino-acids, where very few methods are available. In the table are summarised what are believed to be the most reliable figures for the composition of insulin.

Composition of Insulin.

| Amino-acid. | Nitrogen as % of protein-nitrogen. | Number of residues per molecule. | Ref. |
|--------------------------|---------------------------------------|-------------------------------------|--------|
| Arginine | 6.35 | 2 | 31 |
| Histidine | 8.55 | 4 | 31 |
| Lysine | 3.10 | 2 | 31 |
| Glutamic acid | 11.4 | 15 | 34 |
| Aspartic acid | 4.5 | 6 | 33 |
| Amide-N | 8.95 | 12 | 32 |
| Cystine/2 | 9.36 | 12 | 27 |
| Tyrosine | 6.5 | 9 | 16 |
| Alanine | 4.4, 4.75 | 7 | 30, 35 |
| Valine | 6.0, 6.8 | 8 | 30, 33 |
| Phenylalanine | 4.4, 4.3 | 6 | 30, 33 |
| Serine | 4.45 | 6 | 32 |
| Threonine | 1.57 | 2 | 32 |
| Leucine | 8.95, 9.2 | 12 | 33, 36 |
| <i>iso</i> Leucine | 1.98, 1.83 | 3 | 33, 36 |
| Glycine | 5.2, 5.5 | 7 | 16, 33 |
| Proline | 2.0, 2.3 | 3 | 30, 33 |

The nitrogen accounted for is 98.5% of the total protein nitrogen, indicating that the analysis is almost complete. In assessing the accuracy of the results it must be remembered that it is impossible to carry out a complete control experiment, the chief unknown factor being the breakdown of amino-acids when in peptide form during hydrolysis. In most cases this is probably negligible, but it may be that for certain amino-acids it is different from the breakdown of the free amino-acid. Apart from this

³⁰ *Biochem. J.*, 1946, **40**, 721.

³¹ *Ibid.*, p. 470.

³² *Ibid.*, p. 632.

³³ *Ann. New York Acad. Sci.*, 1946, **47**, 187.

³⁴ A. C. Chibnall, M. W. Rees, and E. F. Williams, *Biochem. J.*, 1943, **37**, 372.

³⁵ A. S. Keston, S. Udenfriend, and M. Levy, *J. Amer. Chem. Soc.*, 1947, **69**, 3151.

³⁶ S. E. Darmon, G. B. B. M. Sutherland, and G. R. Tristram, *Biochem. J.*, 1948,

unknown factor it is probable that the figures for arginine, histidine, lysine, amide-N, serine, and threonine are accurate to 2—3%, and for the other amino-acids to about 5%. The figure for cystine was determined from the total sulphur, which should be accurate to 2%, assuming all the sulphur is in fact in cystine. In column 3 of the table the results have been calculated to the nearest whole number as the number of residues of each amino-acid per insulin molecule of molecular weight 12,000. This gives an overall picture of the composition, and these figures would probably not be affected by the slight errors involved in the analyses.

Besides the amino-acids, crystalline insulin contains a small amount of zinc, which appears to be necessary for the formation of crystals.³⁷ This zinc can be replaced in the crystals by cobalt, nickel, or cadmium.³⁸ Scott and Fisher³⁸ originally estimated the amount of zinc present in crystalline insulin as 0.52% or 3 atoms per unit cell of molecular weight 36,000; however, E. J. Cohn, J. D. Ferry, J. J. Livingood, and M. H. Blanchard³⁹ have shown that, according to the method of crystallisation, amounts of zinc varying from 0.3 to 0.6% could be introduced, but that on repeated washing of the crystals the zinc content fell to about 0.3—0.35%, which corresponds to 2 atoms of zinc per unit cell. Crystals have also been prepared having 0.15% zinc or one atom per unit cell,⁴⁰ so that it would appear that the zinc content cannot be regarded as a reliable constant of insulin. It is only loosely bound to the molecules in solution since it can be completely removed by electrodialysis,³⁹ and it seems doubtful whether it plays any important role in the structure of the active principle.

Further Details of Insulin Structure.—Insulin is exceptional among proteins in that it has a very high content of free α -amino-groups. That at least one of these was located on a phenylalanyl residue was demonstrated by H. Jensen and E. A. Evans,⁴¹ who isolated the phenylhydantoin of phenylalanine from a hydrolysate of insulin that had previously been treated with phenyl isocyanate. In order to obtain more complete information about the free amino-groups of insulin and other proteins and peptides, a method was worked out for the identification and estimation of the amino-acids on which these groups were located using 1-fluoro-2 : 4-dinitrobenzene.⁴² When this method was applied to insulin it was found that two free amino-groups were on phenylalanyl residues, two on glycyl residues, and two on the ϵ -amino-groups of the lysine residues, making a total of six free amino-groups, four of which are α -amino-groups. In this way it has been possible to locate the position of four of the amino-acid residues in insulin in the "terminal" position, and by carrying the method further and using partial hydrolysis it is possible to locate a few more residues which are near to the terminal residues.⁴³ Thus the presence of the following amino-acid sequences

³⁷ D. A. Scott, *Biochem. J.*, 1934, **28**, 1592.

³⁸ D. A. Scott and A. M. Fisher, *ibid.*, 1935, **29**, 1048.

³⁹ *J. Amer. Chem. Soc.*, 1941, **63**, 17.

⁴¹ *Ibid.*, 1935, **108**, 1.

⁴³ *Idem*, *Nature*, 1948 **162**, 491.

⁴⁰ M. Sahyun, *J. Biol. Chem.*, 1941, **138**, 487.

⁴² F. Sanger, *Biochem. J.*, 1945, **39**, 507.

has been demonstrated to occur in insulin: glycyl-isoleucyl-valyl-glutamic acid and phenylalanyl-valyl-aspartyl-glutamic acid, the glycyl and phenylalanyl residues being two of the terminal residues. Using a similar method, D. W. Woolley⁴⁴ has reported the isolation of what appears to be another set of terminal peptides from insulin.

It was suggested⁴² that, since insulin has four free α -amino-groups, it is thus built up of four open polypeptide chains, and that these chains are bound together by the -S-S- bridges of the cystine residues, the only type of cross-linkage that is definitely known to exist in proteins. If this is the true picture of the insulin molecule it should be possible to split it into its separate chains by breaking the -S-S- bridges. This has been accomplished by oxidising them with performic acid to give -SO₃H groups.⁴⁵ The oxidation products, which had a relatively low molecular weight, could be separated into 2 main fractions; an acidic fraction which had only glycine terminal residues, and contained no arginine, histidine, lysine, threonine, or phenylalanine, and a basic fraction which has phenylalanine terminal residues and all the amino-acids that are found in insulin. From the sulphur distribution between the two fractions two structures for the insulin molecule were possible.⁴³ These two structures are shown in Fig. 2, where the full lines represent the peptide chains, and the broken lines the -S-S- bridges. The acid chains with glycyl terminal residues are marked G, and the basic chains with phenylalanyl terminal residues are marked P.

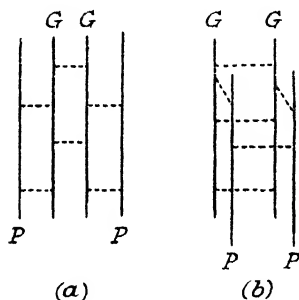


FIG. 2.

Results from experiments with monolayers of insulin suggest that the structure *a* is the most probable. When spread on an air-water interface, insulin forms a monolayer of 7–9 Å. thickness, that is the average thickness of one polypeptide chain,⁴⁶ and the spread material can be recovered in an active form. Structure *b* would not be expected to form a monolayer of this thickness without rupture of an -S-S- bridge, which would not occur on spreading, and would cause inactivation. Thus it would seem that the structure represented in Fig. 2*a* is the most likely structure of insulin, and the simplest way of explaining the facts that have so far been accumulated.

Another method of approaching the problem of insulin structure, which should prove useful, is to break down the molecule in a specific manner with pure proteolytic enzymes and to analyse the structure of the breakdown products. This method has been used by J. A. V. Butler, D. M. P. Phillips, and J. M. L. Stephen,^{47, 48} who showed that, when insulin is

⁴⁴ *Fed. Proc.*, 1948, **7**, 200.⁴⁵ F. Sanger, *Nature*, 1947, **160**, 295.⁴⁶ A. Rothen, B. F. Chow, R. O. Greep, and H. B. van Dyke, *Cold Spring Harbor Symp. quant. Biol.*, 1941, **9**, 272.⁴⁷ *Nature*, 1948, **162**, 418.⁴⁸ J. A. V. Butler, E. C. Dodds, D. M. P. Phillips, and J. M. L. Stephen, *Biochem. J.*, 1948, **42**, 116, 122.

digested with chymotrypsin for a short period, it is broken up into a number of small peptides and a "core," which is precipitable by trichloroacetic acid. This core has a molecular weight of about 5,000, and is electrophoretically homogeneous. It contains 80–90% of the total sulphur of insulin and has no, or only traces of, arginine, proline, threonine, and phenylalanine, and most of the terminal residues are glycine. It thus resembles, in some ways, the acidic fraction obtained by oxidation of insulin, though the exact interpretation of these data is not clear at present.

Relation between Structure and Physiological Activity.—A large amount of work has been done, especially by Freudenberg and his collaborators,^{49, 50, 51, 52} in attempts to determine which groups of the insulin molecule are responsible for its physiological activity. On the assumption that there was some small "active centre" or prosthetic group on the molecule, it was hoped to determine its structure, and obviate the necessity of elucidating the complete structure of the protein. While this hope is still far from being realised, these experiments have shown that certain groups are essential for activity, whereas others are not. The chief method of approach to this problem was to treat the insulin with a reagent, which reacted as far as possible specifically with a single type of group, and to test the activity of the product.

One disappointing conclusion that must be drawn from these experiments is that the intact polypeptide structure of the molecule appears to be essential for physiological activity. In no way has it been possible to split off an active fraction from the rest of the molecule. As soon as any peptide bonds are broken by enzymic^{50, 53, 54} or acid⁴⁹ hydrolysis or any -S-S- bridges are broken by reduction^{52, 55, 56} or oxidation,^{51, 52} the insulin is irreversibly inactivated. This makes the hope of being able to synthesise an active insulin a rather remote one. Treatment of insulin with specific reagents has, however, indicated that not all of the insulin molecule is in fact essential for activity, and suggests that there may be a small active centre on the molecule composed of a number of groupings in a particular arrangement.

When insulin is treated with keten at pH 6, the free amino-groups are completely acetylated in about five minutes, and no other groups appear to have reacted. On prolonged action of keten the phenolic hydroxyl groups of the tyrosine residues also react. K. G. Stern and A. White⁵⁷ showed that if only the amino-groups are acetylated the insulin is still active, whereas acetylation of the phenolic hydroxyl groups causes

⁴⁹ K. Freudenberg, W. Dirscherl, and H. Eyer, *Z. physiol. Chem.*, 1931, **202**, 128.

⁵⁰ K. Freudenberg, W. Dirscherl, H. Eichel, and E. Weiss, *ibid.*, p. 159.

⁵¹ K. Freudenberg and H. Eyer, *ibid.*, 1932, **213**, 226.

⁵² K. Freudenberg and T. Wegman, *ibid.*, 1935, **233**, 159.

⁵³ A. F. Charles and D. A. Scott, *Trans. Roy. Soc. Canada*, 1930, **24**, V, 95.

⁵⁴ A. M. Fisher and D. A. Scott, *J. Biol. Chem.*, 1934, **106**, 289.

⁵⁵ V. du Vigneaud, A. Fitch, E. Pekarek, and W. W. Lockwood, *ibid.*, 1931, **94**, 233.

⁵⁶ K. G. Stern and A. White, *ibid.*, 1937, **117**, 95.

⁵⁷ *Ibid.*, 1938, **122**, 371.

inactivation. This inactivation could be reversed by removing the *O*-acetyl groups with dilute alkali. It thus seems that the free amino-groups are not essential for activity, whereas the phenolic hydroxyl groups are essential. The essential nature of the phenolic hydroxyl groups was also demonstrated by C. R. Harington and A. Neuberg⁵⁸ who showed that, when insulin was iodinated by a method which appeared to substitute only in the tyrosine residues, it was inactivated, and removal of the iodine by reduction caused some reactivation.

Other groups that appear to be essential are the free carboxyl groups. Esterification of these groups by alcohols in the presence of acids causes inactivation, which may be reversed by removal of the ester group in dilute alkali.^{59, 49, 60} Such treatment is believed to be specific for carboxyl groups, and not to cause any splitting of peptide bonds.⁶¹ The inactivation of insulin by diazomethane⁴⁹ is also probably due to reaction with carboxyl groups.

If insulin is treated with concentrated sulphuric acid at -18° , an insulin sulphate is produced, in which the aliphatic hydroxyl groups of the serine and threonine residues are substituted.⁶² This derivative was found to be active,⁶⁰ showing that the aliphatic hydroxyl groups are not essential. This treatment introduced extra acidic groups into the molecule so that it can be concluded that neither the net charge nor the ratio of acidic to basic groups in the molecule is important in determining biological activity.

Several workers have demonstrated that formaldehyde causes the inactivation of insulin,^{51, 63} but the reaction of formaldehyde with proteins is extremely complicated⁶⁴ so that it is difficult to draw any definite conclusions from most of their results. Recently, however, H. Fraenkel-Conrat and H. S. Olcott⁶⁵ have shown that at pH 11–12 formaldehyde reacts irreversibly only with the amido- and the guanidino-groups of the protein. Insulin so treated was still active,⁶⁶ indicating that neither of these groups is essential.

Thus in trying to obtain a picture of the "active centre" responsible for the activity of insulin it would seem that it contains carboxyl and phenolic hydroxyl groups, whereas amino-, aliphatic hydroxyl, amido-, and guanidino-groups are presumably not involved. An intact state of the $-S-S-$ groups and the peptide bonds is probably essential to maintain the specific configuration of the active groupings. No information is available

⁵⁸ *Biochem. J.*, 1936, **30**, 809.

⁵⁹ F. H. Carr, K. Culhane, A. T. Fuller, and S. W. F. Underhill, *ibid.*, 1929, **23**, 1010.

⁶⁰ M. B. Glendening, D. M. Greenberg, and H. Fraenkel-Conrat, *J. Biol. Chem.*, 1947, **167**, 125.

⁶¹ H. Fraenkel-Conrat and H. S. Olcott, *ibid.*, 1945, **161**, 259.

⁶² H. C. Reitz, R. E. Ferrel, H. Fraenkel-Conrat, and H. S. Olcott, *J. Amer. Chem. Soc.*, 1946, **68**, 1024.

⁶³ D. A. Scott, *J. Biol. Chem.*, 1925, **65**, 601.

⁶⁴ D. French and J. T. Edsall, "Advances in Protein Chemistry," 1945, **2**, 278.

⁶⁵ *J. Biol. Chem.*, 1948, **174**, 827.

⁶⁶ H. S. Olcott and H. Fraenkel-Conrat, *Chem. Reviews*, 1947, **41**, 168.

to decide whether the glyoxaline groups of the histidine residues or the non-polar side-chains of the monoamino-acids are essential for biological activity. These latter groups cannot be entirely ignored. Although they cannot be involved in electrostatic or hydrogen bonds they may form specific types of bonds due to van der Waals forces, which may play an important part in specific reactions between large molecules.

F. S.

5. THE CHEMOTHERAPEUTIC APPROACHES TO THE T.B. PROBLEM.

The chemotherapy of tuberculosis implies a simplified concept which may have been compromised in the reader's mind by association with pre-knowledge restricted to the application of successful chemotherapy in other microbial diseases. This is not of itself a bad thing. On the other hand, no other host-parasite relation has been the subject of such detailed enquiry at the hands of pathologists,¹ bacteriologists, chemists,^{2, 3} and others. These studies have emphasised the most destructive nature of the parasitism, the remarkable collaboration of parasite and host in the death of the host's vital tissues, and the unsolved riddle of delayed lysis of caseous tissue with its capacity to spread infection. Appreciation of the unusual pathology of this normally self-limiting chronic disease has emphasised the desirability of approaching the problem of elimination of the parasite on a broad front. It will be convenient for our present purpose first to describe the nature of the biochemical lesions which the observed pathological changes indicate, and from this basis to review the present advances.

Usually, by the time the disease is identified clinically it has established its characteristic pathology, the tubercle, and this is so even in its more acute manifestations.⁴ The minimal clinical lesion visualised, for example, by X-ray shadows, represents destructive changes and reflects, as we shall see, at least two biochemical lesions.

The Origin of the Tubercle and its Ultimate Fate.—The tubercle is the characteristic but not unique lesion of the disease: typical epithelioid cell tubercles are seen in sarcoid, leprosy, tularemia, schistosomiasis, and syphilis. Many studies of all stages of the development of tubercles enable an unequivocal description to be given.^{1a} Within a few minutes of an experimentally induced infection, a normal mononuclear phagocyte ingests a (single) invading tubercle bacillus. The cell increases in size, its nucleus enlarges, and it becomes an epithelioid cell.⁵ Next, fusion of several epithelioid phagocytes takes place to give a Langhans giant cell with its

¹ A. R. Rich, "The Pathogenesis of Tuberculosis," Charles C. Thomas, Springfield, Illinois, 1944.

^{1a} *Idem*, *ibid.*, Chap. 18.

² H. G. Wells and E. R. Long, "The Chemistry of Tuberculosis," Ballière, Tindall, and Cox, 1932.

³ R. J. Anderson, *Physiol. Rev.*, 1932, **12**, 166.

⁴ A. R. Rich and H. A. McCordock, *Bull. Johns Hopkins Hosp.*, 1933, **52**, 5.

⁵ F. R. Sabin and C. A. Doan, *J. Exp. Med.*, 1927, **46**, 627.

numerous nuclei arranged in a "rosette," or there may be formed the less frequent "foreign-body giant cell" in which the nuclei are scattered. Within 3 or 4 days a small nodule is built up by clustering epithelioid cells, shown by Metchnikoff⁶ to be simply altered monocytes. Since the nodule grows progressively after access to blood-borne phagocytes is cut off, it is believed¹ that the phagocytes multiply *in situ*. Gradually the adjacent tissue cells are pushed aside, dying from nutritional deficiencies caused by pressure of the expanding tubercle. At this stage of development collagen fibres are formed between the epithelioid cells. Should multiplication of the bacillus be held in check, no necrosis is observed, and with the death of the tubercle bacilli the transfer to collagen becomes progressive, the tubercle becoming fibrous so that only a nodule of fibrous tissue finally remains. Complete resolution and disappearance of the tubercles has been frequently reported, and this is also true of large tubercles which had proceeded to central caseation in guinea-pigs.⁷ Should multiplication proceed, the central portion dies and becomes necrotic.

Permeability of the Tubercle.—Important from any consideration of chemotherapy is whether tubercles and associated caseous tissue are readily permeable. Rich¹ points to the inherent evidence of viable tubercle bacilli and host cells dependent upon diffusible nutrilites for their continued survival, and to the frequency with which central foci become calcified. Much additional evidence is now available from chemotherapeutic studies with diaminodiphenyl sulphone derivatives such as promin⁸ and sulphetrone⁹ and of the positive evidence of diffusibility derived from successful streptomycin therapy in miliary tuberculosis of man.¹⁰ Brownlee has found sulphetrone to penetrate normal and caseous tissue of man with equal facility.^{10, 11}

Hypersensitivity and Necrosis.—Although the death of host cells appears to follow to some degree the lodgment of the foreign body which the tubercle also is, it is now known that the widespread tissue destruction which characterises the disease follows the conditioned hypersensitivity induced by the products of metabolism of virulent pathogens. The protein component is known to be responsible, and appears to be identical with tuberculin which is harmless to the normal insensitive animal but is a deadly poison to the sensitised host. All that is known of this mechanism confirms the opinion that the clinical disease in all its manifestations follows from the phenomenon of hypersensitivity. Actively multiplying organisms appear to be essential, and virulence in this connection connotes a capacity to multiply.

Caseation.—Liquefaction of body cells after their death is the normal

⁶ W. B. Soper, *Amer. Rev. Tuberc.*, 1917, 1, 385.

⁷ L. U. Gardner, *ibid.*, 1922, 6, 163.

⁸ W. H. Feldman, F. C. Mann, and H. C. Hinshaw, *ibid.*, 1942, 46, 187.

⁹ G. Brownlee and C. R. Kennedy, *Brit. J. Pharmacol.*, 1948, 3, 29.

¹⁰ A. H. Baggenstoss, W. H. Feldman, and C. H. Hinshaw, *Amer. Rev. Tuberc.*, 1947, 55, 54.

¹¹ G. Brownlee, *Lancet*, 1948, ii, 131.

prerequisite for disposal by phagocytes and is a function of proteolytic enzymes contained in the cells. In the characteristic tuberculous lesion, only partial autolysis occurs, and the necrotic cells lose structure, outline, and nuclei to become, together with their intercellular materials, a formless "caseous" mass. Opinion is divided on the reason for incomplete digestion. E. L. Opie and B. I. Barker¹² showed that active enzymic function could be identified with the onset of caseation but subsequently ceased, whether because of absence or inactivation was not proved. J. W. Jobling and W. Petersen¹³ found the soaps of unsaturated fatty acids extracted from tubercle bacilli inhibited *in vitro* the proteolytic activity of the leucocytic enzymes. On the other hand, caseation is characteristically observed in man in infections with micro-organisms which attract *mononuclear* phagocytes, for example, in typhoid but not in the allied colon bacillus infections which attract *polymorphonuclear* phagocytes. It is of great interest that typical caseation follows the necrosis of "lipoid pneumonia" which results from the accidental introduction of, for example, cod-liver oil into the human lung. An outpouring of mononuclear phagocytes characterises these lesions also.^{1a} The predominance of mononuclear phagocytes in caseous lesions induced the comparison of Weiss and Czarnetzky¹⁴ between the proteolytic enzyme activity of the two types of cell. The monocytes of rabbits contained one proteinase, pepsin with an optimal activity at pH 3, whereas the polymorphonuclears contained pepsin, cathepsin, and trypsin with optima at pH 3, 5.4, and 8 respectively.

Softening.—The "softening" of caseous lung substance allows imprisoned tubercle bacilli to be discharged into the air-passages and thus to infect new sites. In contrast to caseous areas, a remarkable characteristic of softened areas is the large number of tubercle bacilli they contain. It seems logical to attribute the lysis of caseous material to enzymic action, but this is unproven. Tubercle bacilli are known to be poor in proteolytic enzyme content,² and the current view appears to attribute the renewed digestion to the activity of infiltrating polymorphonuclear leucocytes which are commonly identified in freshly softening areas.^{15, 1}

Fate of the Caseous Lesion.—Should the tubercle bacilli die, the caseous area may become encapsulated by connective tissue, or it may be resolved. This surprising observation is now well documented.^{16, 17, 18}

Calcification.—The calcium phosphate which is deposited in caseous areas has the same composition, $\text{Ca}_3(\text{PO}_4)_2$, as that of normal bone,² and, apart from the suggestive indications that high serum calcium and phosphorus concentrations influence calcium deposition,¹⁹ as, for example, in

¹² J. Exp. Med., 1914, 19, 645.

¹³ Ibid., p. 383.

¹⁴ C. Weiss and E. J. Czarnetzky, Arch. Path., 1935, 20, 233.

¹⁵ P. Huebschmann, "Pathologische Anatomie der Tuberkulose," Julius Springer, Berlin, 1928.

¹⁶ H. S. Willis, Amer. J. Roentgenol., 1934, 31, 721.

¹⁷ E. H. Oppenheimer, Bull. Johns Hopkins Hosp., 1935, 57, 247.

¹⁸ H. E. Burke, Amer. Rev. Tuberc., 1922, 6, 591.

¹⁹ J. K. Bullock, Amer. J. Dis. Child., 1930, 40, 725.

children generally, and that phosphatase,²⁰ and vitamins A²¹ and D play an important but as yet undisclosed part, no final comment can be made on the conditions governing deposition of calcium in necrotic tissue.

Mode of Action of the Tubercle Bacillus.—We are now in the position to examine three important biochemical reactions conditioned by the host-parasite relation and to enquire further into the activity of the specific substances involved.

(a) The bodies of infecting tubercle bacilli contain substances which resist degradation by the ordinary defensive mechanisms and are treated by the host in an unusual way. Instead of being engulfed by polymorphonuclear leucocytes and carried to the lymph nodes for digestion and elimination they are absorbed *in situ* by monocytes which may subsequently be converted into a tubercle. It is noteworthy that this is the beginning of a usually successful self-limiting process, and it is tempting to regard it as a protective device on the part of the host. Numerous observers^{22, 1} have been sufficiently impressed by the non-toxicity of multiplying virulent tubercle bacilli for normal tissue, or in tissue-culture preparations, to describe the association as symbiosis. Nevertheless, the immunity of the bacillus within the monocyte and, should multiplication ensue, the subsequent production of caseous tissue appear to indicate a common biochemical lesion associated with specific enzyme inhibition.

(b) The tubercle bacillus produces no pharmacological poison, either of exotoxic origin excreted during the life of the bacillus or of endotoxic nature liberated by lysis after its death. Should multiplication ensue, a product of metabolism induces hypersensitivity of adjacent host cells with the result that an otherwise innocuous product becomes a poison responsible for the death of cells. This remarkable host-parasite collaboration is responsible for most of the clinical manifestations of the disease.

(c) During infection the host may develop a capacity to modify the course of the disease—an acquired resistance.

The Chemical Composition of Tubercle Bacilli and the Biological Activity of their Components.—The status of our knowledge concerning chemical composition up to 1932 is collected and admirably summarised by Wells and Long.² Subsequent to this, F. R. Sabin²³ reported the biological effects produced by the lipins fractionated by R. J. Anderson²⁴ and his colleagues from standard strains of acid-fast bacteria²⁴ grown under carefully standardised conditions of synthetic media, choice of containers and conditions of growth. A complete bibliography of this work is available.²⁵ Anderson²⁴ fractionated, under CO₂, the lipin fractions from acid-fast bacteria into a phosphatide extracted by alcohol-ether, an acetone-soluble "fat," and a chloroform-soluble "wax." The amounts extracted and

²⁰ G. H. Bell, *Brit. Med. Bull.*, 1945, **3**, 76.

²¹ (Sir) E. Mellanby, *Proc. Roy. Soc.*, 1944, **B**, **132**, 28.

²² A. A. Maximow, *J. Infect. Dis.*, 1924, **34**, 549.

²³ *Physiol. Rev.*, 1932, **12**, 141.

²⁴ *Ibid.*, p. 166.

²⁵ D. C. White, *Nat. Tuberc. Ass. Series No. 9*, New York, 1929.

TABLE I.
Lipin fractions from acid-fast bacteria.

| | Type of organism. | | | | | | | | | |
|---|-------------------|-------|------------|-------|--------------|-------|---------------|-------|--------------|-------|
| | Human H-37. | | Avian 531. | | Bovine 1698. | | Timothy 02145 | | Leprosy 370. | |
| | G. | %. | G. | %. | G. | %. | G. | %. | G. | %. |
| Phosphatide | 253.1 | 6.54 | 79.7 | 2.26 | 60.5 | 1.55 | 18.7 | 0.59 | 100.5 | 2.20 |
| Acetone-sol- uble fat ... | 240.0 | 6.20 | 77.3 | 2.19 | 131.7 | 3.34 | 87.4 | 2.75 | 289.5 | 6.47 |
| Chloroform- soluble wax | 427.0 | 11.03 | 379.5 | 10.79 | 336.0 | 8.52 | 158.4 | 4.98 | 444.8 | 9.98 |
| Total lipoids | 920.1 | 23.78 | 538.5 | 15.26 | 528.2 | 13.40 | 264.5 | 8.37 | 834.6 | 18.7 |
| Dry bacillary residue..... | 2902.0 | 75.01 | 2942.7 | 83.71 | 3370.1 | 85.50 | 2783.1 | 87.70 | 3389.8 | 80.38 |
| Dry bacterial matter per culture..... | 1,928 | | 1,757 | | 2,318 | | 1,982 | | 1,488 | |

their distribution among acid-fast bacteria are shown in Table I adapted from his account.²⁴ The "wax" fraction is a complex phosphatide; it separates into a high- and a low-melting fraction. The high-melting fraction is hydrolysed with difficulty to give an acid analogous to phthioic acid and a polysaccharide; there is also phosphorus and glycerol. The other fraction yields numerous glycerides of saturated fatty acids of the phthioic acid series. The acetone-soluble "fat" contains neither phosphorus nor nitrogen, and yields a carbohydrate and numerous fatty acids on hydrolysis. The acids present are butyric, palmitic, stearic, cerotic, linoleic, linolenic, tuberculostearic, and phthioic. This acetone fraction proved to be the best source for the characteristic fatty acids of the tubercle bacillus which are present in predominating amounts.

The products of the acid hydrolysis of the phosphatide are given in Table II.

TABLE II.
Cleavage products (%) from bacterial phosphatides.

| | Human. | Avian. | Bovine. | Timothy. | Leprosy. |
|---|--------|--------|---------|----------|----------|
| Total ether-soluble | 66—67 | 55—56 | 57—58 | 60 | 62.2 |
| Palmitic acid | 30.5 | 18.4 | 27.0 | 20.0 | 18.6 |
| Oleic acid after reduction to stearic acid | 12.8 | 18.4 | 7.0 | 5.6 | 13.8 |
| Liquid saturated fatty acids pre- sumably mixtures of tuberculo- stearic and phthioic | 20.9 | 14.1 | 16.0 | 18.0 | 13.5 |
| Total fatty acids recovered | 64.2 | 53.7 | 50.0 | 43.6 | 45.9 |
| Water-soluble constituents | 33—34 | 46—47 | 43—44 | 40.0 | 38.0 |
| Mannose | 9.2 | 13.3 | 6.7 | 9.5 | 5.2 |
| Inositol (inositol) | 8.9 | 3.0 | 3.5 | 2.2 | 0.6 |
| Other sugars | 12.3 | | | | 20.6 |
| Glycerophosphoric acid | 5.4 | 6.0 | 9.9 | 10.0 | |

From the acid hydrolysis of the phosphatide has been obtained a homologue of stearic acid, named tuberculostearic acid, subsequently shown by Spielman to be 10-methylstearic acid, and found to be without biological activity.²³ There were also separated (+)- and (—)-hexacosanic acids,

$C_{26}H_{52}O_2$, named phthioic acid, of which only the (+)-acid had biological activity.²³

Analogous but optically inactive acids with biological activity²³ were extracted from the lipins of avian and bovine tubercle bacilli, and from leprosy bacilli and timothy-grass bacilli.²⁴ There was also evidence of small amounts of higher acids. More recent evidence indicates the presence in human tubercle bacilli of many branched-chain fatty acids not hitherto identified.^{27, 28, 29} N. Polgar³⁰ has presented an improved scheme for separating the acids, which are first converted into acetonyl esters and then into semicarbazones which are then crystallised; from this treatment four new acids emerge. Recent evidence pointed to the likelihood that Anderson's phthioic acid was a mixture, probably of two acids.³¹ N. Polgar and (Sir) R. Robinson³² synthesised a number of methyl-substituted long-chain acids, and a review of the chemical and physical evidence together with the knowledge of its biological activity²³ prompted a preference for 3 : 13 : 19-trimethyltricosanoic acid as "phthioic acid."

Acid-fastness.—A large group of organisms, of which the tubercle bacillus is one, resist decolorisation with acids after being dyed with aniline dyes. This property is retained by the "waxy" fraction, and of that complex by an acid of high molecular weight named "mycolic acid."^{24, 54} Certain evidence points to the fact that the physicochemical state of mycolic acid within the bacillus contributes to acid-fastness.^{55, 56}

Biological Properties of the Isolated Lipins.—In the hands of Sabin and her colleagues^{34, 35, 23} all three of Anderson's²⁴ lipin fractions, but no other fraction, protein or carbohydrate, produced tubercles. Of these the phosphatide was most active in giving epithelioid giant cells and subsequent caseation, and this applied to phosphatide from human, avian, bovine, timothy-grass, and lepra bacilli, in that order of biological activity.²³ The only other substance among the controls which "acts just like the tuberculo-phosphatide"²³ is lecithin. Tuberculostearic acid was found to be irritating but did not produce tubercles. (+)- but not (−)-Phthioic acid produces typical tubercles. Sabin²³ has refuted the suggestion of C. H. Boissevain and C. T. Ryder³⁶ that bacillary debris accounted for the phosphatide activity. Still others³⁷ are critical of the specific activity of the phosphatide being attributable to phthioic acid. Of more moment is the criticism of Rich¹ who points to the disproportionate amounts of phosphatide and

²⁷ C. O. Edens, M. M. Creighton, and R. J. Anderson, *J. Biol. Chem.*, 1944, **154**, 587.

²⁸ R. L. Peck and R. J. Anderson, *ibid.*, 1941, **138**, 135.

²⁹ L. G. Genger and R. J. Anderson, *ibid.*, 1944, **156**, 443.

³⁰ *Biochem. J.*, 1948, **42**, 206.

³¹ Sir R. Robinson, personal communication, 1949.

³² *J.*, 1945, 389.

³³ J. Ungar, C. E. Coulthard, and L. Dickenson, *Brit. J. Exp. Path.*, 1948, **29**, 322.

³⁴ F. R. Sabin, C. A. Doan, and C. E. Forkner, *J. Exp. Med.*, 1930, **52**, suppl. 3.

³⁵ F. R. Sabin, K. C. Smithburn, and R. M. Thomas, *ibid.*, 1935, **62**, 771.

³⁶ *Amer. Rev. Tuberc.*, 1931, **24**, 751.

³⁷ K. Bloch, *Biochem. Z.*, 1936, **285**, 372.

phthioic acid needed to produce tubercles and caseation compared with the observable depredations of a single bacillus. For example, the phosphatide from 300 mg. of bacilli produced a little caseation in 1 of 4 guinea-pigs injected intraperitoneally and in each of two receiving the amount from 8.0 g. of bacilli.³⁸ More recently Ungar, Coulthard, and Dickenson³³ found the synthetic 3 : 13 : 19-trimethyltricosanoic acid of Polgar and Robinson³² to be more active than crude (+)-phthioic acid from human tubercle bacilli in the production of tubercle-like granulomata which "corresponded in some respects to the description by Sabin, Doan, and Forkner."³⁴ Of 15 synthetic acids tested, 10 were as active as or more active than the natural product. The most active synthetic substance was 3 : 12 : 15-trimethyldocosanoic acid which showed granulomata with as little as 10–25 mg. in a single intraperitoneal dose suspended in aqueous alcohol. The surface layer of precipitated phthioic acid analogues is no doubt very different from that of the continuous film of the intact bacillus. Realisation of this fact prompted J. Ungar³⁹ to observe the chemiotactic response of macrophages to agar blocks in which these acids were entrained and then subsequently implanted in the peritoneal cavity of guinea-pigs. The first cells to penetrate were polymorphonuclear leucocytes and lymphocytes; then came monocytes which engulfed the particles and became typical epithelioid cells. Ungar has made some preliminary observations which if confirmed will shed light on the quantitative aspect of the responses of phthioic acid and its analogues.³⁹ He coated killed colon bacilli with 3 : 13 : 19-trimethyltricosanoic acid, and injected the suspension intraperitoneally into guinea-pigs; the subsequent granulomata of the omentum and elsewhere were indistinguishable from those of killed tubercle bacilli simultaneously injected into controls, and differed entirely from the minor reactions observed in control animals injected with suspensions of colon bacilli.

Biological Significance of the Carbohydrates.—Appreciation of the immunological significance of the bacterial carbohydrate of the pneumococcus as a result of the studies of Avery and Heidelberger, and in particular the association between host-virulence and kind of capsular carbohydrate, the relation between pneumococcal anaphylactic hypersensitivity and carbohydrate, and the demonstration that effective immunity to the pneumococcus is that developed against the carbohydrate has directed interest to the carbohydrate content of the tubercle bacillus.

The tuberculo-carbohydrates isolated by Johnson, Coghill, Brown, and Renfrew,²³ the polysaccharides isolated from the lipins by Anderson,²⁴ and the carbohydrate isolated from media by Long and Seibert²³ were studied by Sabin.²³ Their biological activities appeared to be restricted to a chemiotactic and damaging effect on leucocytes. It has no power to induce hypersensitivity,⁴⁰ but can act as a hapten.⁴¹ That is to say, unlike

³⁸ K. C. Smithburn and F. R. Sabin, *J. Exp. Med.*, 1932, **56**, 862.

³⁹ Personal communication, 1949.

⁴⁰ F. R. Sabin, A. L. Joyner, and K. C. Smithburn, *J. Exp. Med.*, 1938, **68**, 563.

⁴¹ P. P. Laidlaw and H. N. Dudley, *Brit. J. Exp. Path.*, 1925, **6**, 197.

the pneumococcus-specific carbohydrate,^{42, 43} the tuberculo-carbohydrate does not stimulate antigen formation, or induce protection, but is capable of reacting in precipitin tests with sera from infected hosts.⁴¹ A critical biological re-examination of the three different specific polysaccharides is overdue. M. Heidelberger and A. E. O. Mizel⁶⁹ found the principal serologically active cell component ($[\alpha]_D +85^\circ$) to contain D-arabinose and D-mannose, and later found a second specific somatic polysaccharide of lower dextrorotation.^{70, 71} (Sir) N. Haworth, P. W. Kent, and M. Stacey^{72, 73} similarly isolated a somatic polysaccharide of $[\alpha]_D^{18^\circ} +85^\circ$ together with a deoxyribonucleic acid derivative and glycogen and, also, a polysaccharide of $[\alpha]_D^{18^\circ} +25^\circ$ closely associated with the cell lipins.

Biological Significance of the Proteins of the Tubercle Bacillus.—A number of proteins have been extracted from the tubercle bacillus²⁴ and one from the medium in which it is grown.² In their purest forms these proteins have practically no toxicity for the uninfected body,⁴⁴ but are lethal in extremely small doses for the tuberculous subject, as was first demonstrated by Koch for impure "tuberculin."⁴⁵ The innocuous nature of purified tuberculoprotein for non-sensitised cells was demonstrated in an elegant way in tissue-culture preparations by Rich and Lewis⁴⁶ and contrasted with its lethal effect on similar cells from tuberculous hypersensitive animals.^{46, 47, 48} Thus, although innocuous for the normal, it is highly toxic for the tuberculous hypersensitive body, causing necrosis, fever, severe constitutional symptoms and even death.¹ These facts, first demonstrated by Koch,⁴⁵ have been repeated many times⁴⁹ and have been redemonstrated in a most convincing fashion by Seibert,⁴⁹ using "pure" tuberculin.⁵⁰ Thus while hypersensitivity is demonstrably a response to protein within the bacillus no convincing evidence has been offered that this hypersensitivity can be induced in the *normal* animal with the protein itself. Only whole bacilli, living or dead, successfully initiate tuberculin hypersensitivity.¹ The tuberculoproteins are antigenic,^{51, 52, 53} but they have no protective capacity.

Acquired Resistance.—While infection with the tubercle bacillus does not confer the stable and solid protection acquired after diphtheria or smallpox, there is little doubt that a significant degree of protection is

⁴² O. T. Avery and W. F. Gobel, *J. Exp. Med.*, 1933, **58**, 731.

⁴³ L. D. Felton, *U.S. Publ. Health Repts.*, 1938, **63**, 1855.

⁴⁴ F. B. Seibert and B. Munday, *Amer. Rev. Tuberc.*, 1931, **23**, 23.

⁴⁵ R. Koch, *Deut. med. Woch.*, 1891, **17**, 101.

⁴⁶ A. R. Rich and M. R. Lewis, *Bull. Johns Hopkins Hosp.*, 1932, **50**, 115.

⁴⁷ J. D. Aronson, *J. Exp. Med.*, 1931, **54**, 387.

⁴⁸ J. K. Moen and H. F. Swift, *ibid.*, 1936, **64**, 339.

⁴⁹ E. R. Long and F. B. Seibert, *Amer. Rev. Tuberc.*, 1926, **13**, 448.

⁵⁰ F. B. Seibert, *ibid.*, 1941, **44**, 1.

⁵¹ F. B. Seibert, *ibid.*, 1930, **21**, 370.

⁵² L. Deinnes, *J. Immunol.*, 1929, **17**, 85.

⁵³ M. Pinner, *Amer. Rev. Tuberc.*, 1923, **18**, 497.

⁵⁴ F. H. Stodola, A. Lesuk, and R. J. Anderson, *J. Biol. Chem.*, 1938, **126**, 505.

⁵⁵ T. H. C. Benians, *J. Path. Bact.*, 1912, **17**, 199.

⁵⁶ H. Sherman, *J. Infect. Dis.*, 1913, **12**, 249.

attained.¹ Although widespread agreement exists that the living, attenuated bovine bacillus of Calmette (BCG)⁵⁸ confers recognisable acquired resistance in laboratory animals, there has been more reluctance to accept the claims for heat-killed tubercle vaccine. A meticulous and critical reviewer like Rich,¹ writing in 1944, speaks of the established fact doubted for years, and quotes numerous successful investigators,^{59, 60, 61, 62} yet S. Raffel⁵⁷ is unable to satisfy himself that a heat-killed vaccine confers resistance. In the Reporter's laboratory, G. Brownlee and C. R. Kennedy⁶³ found the A. S. Griffith and R. E. Glover's glycerol-killed vaccine⁶⁴ to be little less effective than a BCG living vaccine.

TABLE III.

Immunological responses in guinea-pigs to the attenuated tubercle bacillus, and a tubercle vaccine and its chemical fragments.

| Preparation injected. | Acquired resistance. | Purified tuberculin responses. | Biochemical lesion associated with. |
|--|----------------------|--------------------------------|---|
| 1. BCG ⁵⁸ | + | + | a. Acquired resistance ⁶⁵ b. Chemiotaxis of monocytes ^{1, 22, 65} c. Inhibition of proteases ¹⁴ d. Hypersensitivity and induced lethal effect ^{45, 1} e. Skin allergy ⁵⁷ |
| 2. Suitably prepared vaccine ^{59, 60, 61, 62, 63} | + | + | As 1 above |
| 3. "Wax" ²⁴ | — | + | a. Chemiotaxis to monocytes ^{23, 33, 39} b. Inhibition of proteases ¹⁴ c. Skin allergy ⁵⁷ |
| 4. Phosphatide ²⁴ | — | — | As 5 below |
| 5. "Phthioic acid" ^{24, 30, 31, 32} | — | — | a. Chemiotaxis to monocytes ^{23, 33, 39} b. Inhibition of proteases ¹⁴ (? inhibited β -oxidation ⁶⁶) |
| 6. Crystalline protein ^{1, 51} | — | — | a. Hypersensitivity and induced lethal effect ^{45, 1} |
| 7. Polysaccharide ^{23, 24} | — | — | a. Chemiotaxis of leucocytes ²³ |

* "Wax" contains bound protein.¹

Elimination of the Parasite.—Indirect approach. Attempts to demonstrate acquired resistance with BCG and killed vaccine in the laboratory animal (Table III) have probably also been successful for man (BCG⁶⁵) (killed vaccine⁶⁷). However, no recombination of the known chemical fragments has yet proved successful. It appears that the antigenic complex which confers resistance is labile and readily destroyed by chemical mani-

⁵⁷ *Amer. Rev. Tuberc.*, 1946, **54**, 564.

⁵⁸ A. Calmette, *Bull. Inst. Pasteur*, 1924, **22**, 593.

⁵⁹ A. Boquet and R. Laporte, *Compt. rend. Soc. Biol.*, 1937, **124**, 1159.

⁶⁰ W. Pagel, *J. Path. Bact.*, 1937, **44**, 643.

⁶¹ R. M. Thomas, *J. Exp. Med.*, 1933, **58**, 227.

⁶² B. Lange, R. Freund, and E. Jochimsen, *Z. Hyg.*, 1927, **107**, 426.

⁶³ Unpublished data, 1949.

⁶⁴ *J. Comp. Path.*, 1939, **52**, 57.

⁶⁵ K. N. Irvine, "The B.C.G. Vaccine," Oxford University Press, London, 1934.

⁶⁶ Sir R. Robinson, *Nature*, 1946, **158**, 815.

⁶⁷ G. G. Kayne, *Amer. Rev. Tuberc.*, 1936, **34**, 10.

pulation. Renewed attempts, as, for example, by the extraction of living cells with urea solutions, probably at low temperatures, appear justified. The synthetic or semisynthetic approach may prove amenable, since the identification of the precise chemical causal agent associated with the biochemical lesion observed in the tubercle may have already occurred in the substance at present labelled 3 : 13 : 19-trimethyltricosanoic acid,³² but of greater significance is the uncovering of synthetic analogues of enhanced biological activity.^{33, 66} Similarly the lipin-bound polysaccharide of Sir N. Haworth, P. W. Kent, and M. Stacey⁷² appears to be a hapten⁴¹ of high specificity, and the crystalline protein of Seibert is a known antigen.^{51, 52, 53}

Artificial Antigens.—Not only can the specific acids, protein, and carbohydrate of the parasite be recombined, but they can be linked, individually or in combination, to antigenically significant proteins, with the object of improving upon the natural antigen which confers active resistance. In these reactions, not only the protein carrier but the nature of the chemical linkage has proved significant. Landsteiner successfully applied Pauly's reaction^{74, 75, 76} to couple proteins with diazonium compounds and obtained chemically defined specificities. This has proved a very flexible method but has been criticised as yielding an unnatural linkage. S. H. Hopkins and A. Wormall^{77, 78, 79} coupled isocyanate derivatives of the hapten to protein at a pH near neutrality to give substituted ureas, and in yet another approach L. Pillemer, E. E. Ecker, and J. R. Wells⁸⁰ introduced haptens to proteins the disulphide groups of which had been reduced to thiol, a method applicable to a cystine-containing protein like tuberculin. Harington and his colleagues^{81, 82, 83} coupled haptenazides to the amino-group of protein so that the final link was of a peptide nature. A stimulating known example of non-specific protection is that given by the antigens containing azobenzyl glucosides of the synthetic gentiobiuronic, cellobiuronic, and glucuronic acids which evoke in rabbits the production of antibodies capable of conferring passive immunity in mice against multiple lethal doses of virulent Type II pneumococci without specific agglutinins or precipitins being demonstrable in the rabbit antisera.⁸⁸ It has been clearly demonstrated that antibodies raised in response to injected antigens need not be protective, as is the case with the known chemical fragments of the tubercle bacillus, and, conversely, as shown by the anti-

⁶⁶ A. Boquet and L. Nègre, *Ann. Inst. Pasteur*, 1923, **37**, 787.

⁶⁹ *Proc. Soc. Exp. Biol. N.Y.*, 1932, **29**, 631.

⁷⁰ M. Heidelberger and A. E. O. Menzel, *J. Biol. Chem.*, 1937, **118**, 79.

⁷¹ *Idem, ibid.*, 1939, **127**, 221.

⁷² *J.*, 1948, 1211, 1220.

⁷⁴ A. Pauly, *Z. physiol. Chem.*, 1904, **42**, 508.

⁷⁵ *Idem, ibid.*, 1905, **44**, 159.

⁷⁶ *Idem, ibid.*, 1915, **94**, 284.

⁷⁷ *Biochem. J.*, 1933, **27**, 740.

⁷⁸ *Ibid.*, p. 1706.

⁷⁹ *Ibid.*, 1934, **28**, 227.

⁸⁰ *J. Exp. Med.*, 1939, **69**, 191.

⁸¹ R. F. Clutton, C. R. Harington, and M. E. Yuill, *Biochem. J.*, 1938, **32**, 1111.

⁸² *Idem, ibid.*, p. 1119.

⁸⁸ G. C. Butler, C. R. Harington, M. E. Yuill, and A. A. Miles, *ibid.*, 1940, **34**, 838.

hormones,^{84, 85, 86, 87} the neutralisation of physiological activity need not be associated with *in vitro* demonstration of the characteristic properties of an antigen. This is unfortunate since protection experiments with tubercle-bacilli infections are costly and very time-consuming.

In the Reporter's laboratory, G. Brownlee and R. Friedmann⁸⁹ prepared artificial antigens from oleic, palmitic, and stearic acid, and from "phthioic acid" and "total phthioic-like acid." Well-defined crystalline azides were obtained with stearic and palmitic acid, and these were coupled to horse-serum globulin and to the high-sugar fraction of albumen,⁹⁰ and also, for absorption tests, to gelatin. Although the complexes were antigenic, they retained no hapten specificity. Oleic acid, "phthioic acid," and "total phthioic-like acids" did not give identifiable azides, but gave complexes by coupling their acid chlorides to the same protein carriers at an alkaline pH. Of these, probably only the "total-phthioic-like acids" and oleic acid retained hapten specificity, and oleic acid was best.

Four of these antigens, BCG living vaccine, H₃₇RV glycerol-killed vaccine, oleic acid-globulin, and "total phthioic acid-like acids" formed the basis of a guinea-pig protection comparison. The infecting strain was a virulent human tubercle bacillus, "Carstairs"—H₃₇RV was deliberately avoided—which gave an average infected life of 30 weeks in the control animals. The final basis of comparison was a "tuberculosis index"⁹¹ based upon the distribution of the disease in affected organs and its histological significance in addition to factors like duration of infected life. The artificial antigens were without protective action, while the BCG and the glycerol-killed H₃₇RV vaccine conferred similar and significant resistance.

Arising out of considerations of the metabolic requirements of bacteria of the acid-fast group, more fully discussed below, it appears^{92, 93} that naphthaquinones may be implicated. The possibility of interference with essential metabolites or growth factors on the basis of substrate competition is now well appreciated,^{94, 95} but the possible intervention of antibodies raised *in vivo* in response to artificial antigens containing the metabolite as hapten is an alternative weapon.

With the starting point of phthiocol, the yellow pigment of human tubercle bacilli,^{96, 97} G. Brownlee and R. Friedmann⁹⁸ prepared albumen,

⁸⁴ B. Zondek and F. Sulman, *Proc. Soc. Exp. Biol. N.Y.*, 1937, **37**, 343.

⁸⁵ M. Van den Ende, *J. Endocrinol.*, 1941, **2**, 403.

⁸⁶ G. B. Collit, H. Selye, and D. L. Thompson, *Biol. Rev.*, 1940, **15**, 1.

⁸⁷ H. L. Thompson, *J. Exp. Res.*, 1922, **43**, 37.

⁸⁸ W. F. Goebel, *J. Exp. Med.*, 1940, **72**, 33. ⁸⁹ Unpublished data.

⁹⁰ L. F. Hewett, *Biochem. J.*, 1937, **31**, 1047.

⁹¹ G. Brownlee and C. R. Kennedy, *Brit. J. Pharmacol.*, 1948, **3**, 37.

⁹² F. W. Twort and G. L. Ingram, "Johne's Disease," Ballière, Tindall and Cox, London, 1913.

⁹³ D. W. Woolley and J. R. McCarter, *Proc. Soc. Exp. Biol. N.Y.*, 1940, **45**, 357.

⁹⁴ D. D. Woods, *Brit. J. Exp. Path.*, 1940, **21**, 74.

⁹⁵ P. Fildes, *Lancet*, 1940, i, 955.

⁹⁶ R. J. Anderson and M. S. Newman, *J. Biol. Chem.*, 1933, **103**, 197.

⁹⁷ *Idem, ibid.*, 1940, **136**, 211.

⁹⁸ Unpublished data.

globulin, gelatin, and egg-albumen antigens to a series of 12 synthetic analogues of phthiocol. Hapten specificity was probably never encountered in this series, and no compound was subjected to animal protection experiments.

Direct Approach.—"Protective capsule." The slow growth of the tubercle bacillus, its marked hydrophobic properties, and its persistence in the host have raised a concept of a continuous protective lipid capsule.^{1, 2} Yet, after a first isolation on an egg-enriched medium, freshly isolated tubercle bacilli grow on a simple medium containing glycerol as a carbon source, asparagine as a source of nitrogen, phosphates, and a magnesium salt.^{99, 100} Inexact in its nutritional requirements, the *adapted* organism appears to restrict its growth factors to magnesium and phosphorus, which together with an alcohol and an aliphatic amino-acid (amide), water, and oxygen, all readily diffusible water-soluble substances of poor lipin-solubility, constitute its needs. There is, however, little doubt that the lipin-protein-carbohydrate complex constituting the cytoplasmic matrix is capable of resisting the passage of quite simple ions into the cell, since the tubercle bacillus maintains its internal environment within a very broad range of acidity and basicity.¹⁰¹ Contact with 10% sulphuric acid for an indefinite period does not kill, 18% hydrochloric acid kills in 5 hours and 1% in 24 hours, while 5% acetic acid kills in less than 30 minutes.¹⁰² Equally impressive concentrations of bases are required to kill; 32% sodium hydroxide in 24 hours, or 40% in 4 hours. Barium and calcium hydroxide similarly are non-lethal.¹⁰² Phospholipins inhibit the toxic action of many antiseptics on bacteria; ¹⁰³ for example, small amounts of cephalin protect Gram-positive bacteria against gramicidin *in vitro* and *in vivo*, and histones or protamines are able to combine chemically with active groupings of the lipid complex of Gram-negative bacilli and thus render them susceptible to tyrothricin or typical detergents which are otherwise inactive in these conditions.¹⁰³

In vitro Tests.—There is poor correlation between *in vitro* tests for antiseptic activity and subsequent chemotherapy, a problem which is aggravated by the slow growth and unexact metabolic requirements of the tubercle bacillus.^{2, 101, 102} R. J. Dubos ¹⁰³ contrasts the few substances active *in vivo*, and notes the limited, delicate, specific injury, directed, in those cases of which meagre information is available, against anabolic, synthetic processes, or steps in cellular division. In contrast, the bludgeon of antiseptics is directed to catabolic processes, or to anabolic and catabolic indiscriminately. Reliance upon *in vitro* test alone would have preferred aromatic amines and nitroso-derivatives to sulphonamides, toxic quinones

⁹⁹ Proskauer and Beck, from W. H. Feldman and H. C. Hinshaw, *Amer. Rev. Tuberc.*, 1945, **51**, 582.

¹⁰⁰ E. R. Long and F. B. Seibert, *ibid.*, 1926, **13**, 393.

¹⁰¹ H. B. Richardson, E. Shorr, and R. O. Loebel, *Trans. Nat. Tuberc. Ass. N.Y.*, 1931, 205.

¹⁰² C. O. Guss and M. O. Kloetzel, *Nat. Res. Coun. Lit. Survey, U.S.A.*, 1948.

¹⁰³ "The Bacterial Cell," Harvard University Press, 1945.

and phenols to penicillin, and tyrocidine to gramicidin, and would have rejected arsphenamine out of hand.¹⁰³ Older methods of increasing the growth-rate involved enrichment of the medium^{104, 105} and more recently R. J. Dubos^{106, 107} demonstrated that oleic acid in the form of a sorbitan ester or combined with albumen promoted rapid diffuse growth. A less desirable attack on the same problem is the substitution of other rapidly growing organisms for the tubercle bacillus¹⁰⁸ as test objects. R. L. Mayer¹⁰⁹ has similarly suggested the use of members of the family of fungi included under the *Actinomycetes*, but most workers have been unwilling to substitute any organism for the human tubercle bacillus.¹¹⁰ A second inherent disadvantage of the *in vitro* test is the unwillingness of the organism to reproduce in unfavourable circumstances. G. P. Youmans¹¹¹ introduced a method whereby established growth in the shape of very large suspensions is exposed to prepared drug dilutions, and, in both submerged and surface culture, growth therefrom is measured.

***In vivo-in vitro* Test.**—A test which appears to overcome many of the disadvantages of the *in vitro* test was described by Brownlee.¹¹⁰ A toxic dose of the test substance or the largest amount which can be introduced, whichever is smaller, is injected intraperitoneally in oil or other suitable suspension into a guinea-pig of about 550 g. After two hours, or before if the animal shows symptoms, it is anæsthetised with chloroform, the thorax is opened, and about 3 c.c. of blood is drawn aseptically from the still beating heart. The citrated blood is diluted in serial increments with equal volumes of Long's agar contained in previously stoppered Lambeth tubes. These are "sloped" and sown with one drop (0.01 c.c.) of a uniform suspension of tubercle bacilli containing 0.5 mg. per c.c. Incubated at 37.5°, the degree of inhibition, compared with that due to a standard substance such as diaminodiphenyl sulphone or streptomycin, enables a practical answer to be given with avian strains in 6 days and with bovine and human strains in 21 days. The test seems to have the following advantages. The chemotherapeutic activity of the blood is directly measured in terms of a standard substance of known chemotherapeutic activity. Usually it is possible to determine the blood concentration microbiologically or chemically, and in other cases the observation rests on the practical basis of a blood concentration which is optimum since it produces symptoms of acute toxicity or is derived from the maximum quantity it is possible to inject.

***In vivo* Tests.**—Several established animal tests are in use¹¹⁰ such as those with guinea-pigs, mice, or hamsters, the last two in an attempt to reduce the time factor. H. Schwabacher and G. S. Wilson¹¹² intro-

¹⁰⁴ H. Cooper and N. Myei, *J. Lab. Clin. Med.*, 1928, **13**, 469.

¹⁰⁵ R. D. Herrold, *J. Infect. Dis.*, 1931, **48**, 236.

¹⁰⁶ *Proc. Soc. Exp. Biol. N.Y.*, 1945, **58**, 361.

¹⁰⁷ *J. Exp. Med.*, 1946, **83**, 409.

¹⁰⁸ P. D'Arcy Hart, *Brit. Med. J.*, 1946, **II**, 805.

¹⁰⁹ *Rev. Medicale*, 1941, Nov.—Dec. 3.

¹¹⁰ G. Brownlee, *Rept. Internat. Cong. Microbiol.*, 1947, 209.

¹¹¹ *Tubercle*, 1944, **18**, 442. ¹¹² *Proc. Soc. Exp. Biol. N.Y.*, 1937, **57**, 119, 122.

duced the mouse test in which an acute infection is established by huge numbers of tubercle bacilli given intraperitoneally or, more usually, intravenously. The ultimate assessment may be the mean mortality time of the group or the number of organisms recovered from a weighed piece of spleen, and in general some statistical manipulation is essential for interpretation. By exposing groups of mice to a dry mist containing tubercle bacilli, R. E. Glover¹¹³ established a chronic infection restricted to the upper respiratory tract which has proved successful for screening chemotherapeutic drugs. The guinea-pig test is widely used,^{91, 114, 115} and in the classical series of researches of Feldman and his colleagues¹¹⁶ has become a precise tool. It is usual so to design the experiment that a proportion of survivors in a treated group is compared with no survivors in an untreated group. Most workers insist on observing the survivors during the course of their natural lives. A further refinement is to continue treating a proportion of the survivors. The final assessment is preferably in terms of a tuberculosis index in which the distribution and microscopic nature of the lesions figure prominently.

Chemotherapeutic Screening.—In 1932 Wells and Long² assembled the existing knowledge of chemotherapy of tuberculosis and concluded that no known remedy modified the disease in the experimental animal or man. These authors concluded: "A specific chemotherapy of tuberculosis has not been found and it may be a long time in coming because of the inherent difficulties of the problem, but it is not a closed chapter. We have some definite facts to go on, and some glimpses of light have been seen. Probably some new success with some other bacterial infection will be needed to stimulate a new attack on the more difficult problem offered by tuberculosis." G. Domagk's¹¹⁷ very great discovery of the chemotherapeutic activity of "prontosil rubrum" against experimental infections due to virulent streptococci provided the new impetus. The discovery and evaluation of the chemotherapeutic activity of diaminodiphenyl sulphone,¹¹⁸ and the demonstration of its high antibacterial activity to tubercle bacilli by N. Rist,¹¹⁹ provided the next step. The chronic toxicity of the parent substance (not its insolubility, for toxic blood levels are only too readily obtained) prompted the preparation of weighted derivatives. Promin (sodium *pp'*-diaminodiphenyl sulphone *NN'*-diglucosesulphonate) gave more encouraging results in guinea pigs than hitherto observed,¹²⁰ but clinical

¹¹³ *Brit. J. Exp. Path.*, 1944, **25**, 141.

¹¹⁴ M. J. Smith and W. T. McClosky, *Publ. Health Repts. Wash.*, 1945, **60**, 1129.

¹¹⁵ F. T. Calloman, J. A. Kolmer, A. M. Rule, and A. J. Paul, *Proc. Soc. Exp. Biol. N.Y.*, 1946, **63**, 237.

¹¹⁶ W. H. Feldman and H. C. Hinshaw, *Amer. Rev. Tuberc.*, 1945, **51**, 582.

¹¹⁷ *Deut. med. Woch.*, 1935, **61**, 829.

¹¹⁸ G. A. H. Buttle, D. Stephenson, S. Smith, T. Dewing, and G. E. Foster, *Lancet*, 1937, *i*, 1331.

¹¹⁹ *Compt. rend. Soc. Biol.*, 1939, **130**, 972.

¹²⁰ W. H. Feldman, H. C. Hinshaw, and H. E. Moses, *Proc. Mayo Clin.*, 1940, **15**, 695.

studies were disappointing.^{121, 122} Of a series^{123, 124} of sulphones tested disodium formaldehyde sulfoxylate diaminodiphenyl sulphone, diazone,¹²⁵ and promizole (*p*-aminophenyl 5-amino-2-thiazolyl sulphone),¹²⁶ were carried to clinical trial, and the last is still under observation.¹²⁷ Sulphetrone [a sodium tetrasulphonate of di-(*p*-3-phenylpropylaminophenyl) sulphone] proved to be comparable in activity to promin in the guinea-pig,¹²⁸ and remarkably free from chronic toxicity.¹²⁹ Applied to man, it may have a use in certain forms of exudative tuberculosis of the lungs,^{130, 131, 132} but its final status is unknown. It is synergic in action with streptomycin,¹³³ combined therapy with which shows promise in miliary tuberculosis and tubercular meningitis.¹³⁴ Sulphetrone appears to be the most useful chemotherapeutic agent at present known in the treatment of the allied disease, leprosy.¹³⁵

The chemotherapeutic sulphones appear to owe their mode of action to substrate competition, since their activity is inhibited by *p*-aminobenzoic acid, P.A.B.¹²⁹ J. Lehmann's introduction of 4-aminosalicylic acid to tuberculosis¹³⁶ deserves special attention, since it illustrates the successful use of a metabolic approach. Lehmann repeated the observation of F. Bernheim¹³⁸ that benzoates and salicylates increased the oxygen uptake of tubercle bacilli, and noted that this was a feature of pathogenic strains only. On the assumption that benzoates or salicylates might be active as essential metabolites, Lehmann¹³⁷ sought for competitive inhibitors. Of 50 benzoic acid derivatives examined by microrespiration methods, 4-aminosalicylic acid (*p*-aminosalicylic acid, P.A.S.) proved the most effective in inhibiting catabolic oxygen utilisation. The effect was abolished if the amino-group was placed in positions 3 or 5 or if replaced by nitro-. Introduction of methyl or stearyl into the 4-amino-group reduced the activity slightly. If the hydroxyl group in the 2-position was replaced by methyl, activity was retained, but not if it was replaced by amino- or chlorine. Substitutions in the hydroxyl group decreased the activity considerably. Placing the hydroxyl group in position 3 instead of 2 diminished the effect.

¹²¹ H. C. Hinshaw, K. H. Pfuete, and W. H. Feldman, *Amer. Rev. Tuberc.*, 1944, **50**, 52.

¹²² G. Zucker, M. Penner, and H. T. Hyman, *ibid.*, 1942, **46**, 277.

¹²³ W. H. Feldman and H. C. Hinshaw, *Amer. J. Clin. Path.*, 1943, **13**, 144.

¹²⁴ M. I. Smith, E. W. Emmant, and B. B. Westfall, *J. Pharmacol.*, 1942, **74**, 163.

¹²⁵ F. T. Calloman, *Amer. Rev. Tuberc.*, 1943, **47**, 97.

¹²⁶ W. H. Feldman, H. C. Hinshaw, and F. C. Mann, *Proc. Mayo Clin.*, 1944, **19**, 25.

¹²⁷ H. C. Hinshaw, W. H. Feldman, and K. H. Pfuete, *ibid.*, p. 25.

¹²⁸ G. Brownlee and C. R. Kennedy, *Brit. J. Pharmacol.*, 1948, **3**, 29.

¹²⁹ G. Brownlee, A. F. Green, and M. Woodbine, *ibid.*, p. 15.

¹³⁰ T. Anderson and S. J. Strachan, *Lancet*, 1948, *ii*, 135.

¹³¹ D. G. Madigan, *ibid.*, p. 174.

¹³² M. G. Clay and A. C. Clay, *ibid.*, p. 180.

¹³³ G. Brownlee and C. R. Kennedy, *Brit. J. Pharmacol.*, 1948, **3**, 37.

¹³⁴ D. G. Madigan, P. N. Swift, G. Brownlee, and G. P. Wright, *Lancet*, 1947, *ii*, 897.

¹³⁵ E. Muir, *Trans. Roy. Soc. Trop. Med.*, 1948, January 15th.

¹³⁶ *Lancet*, 1946, *i*, 14.

¹³⁷ *Ibid.*, p. 15.

¹³⁸ *J. Bact.*, 1941, **41**, 387.

Replacing the carboxyl group by a sulphonic acid group abolished the effect. Substitutions in the carboxyl group (methyl, ethyl, and furfurylanhydride) changed the activity slightly. Two molecules of 4-aminosalicylic acid linked at position 3 were as effective as 4-aminosalicylic acid but highly toxic to animals. G. P. Youmans^{139, 140} found P.A.S. to be bacteriostatic and moderately suppressive of experimental tuberculosis in mice. Others have described the examination of large series of allied compounds without uncovering greater activity.^{140, 141} The partial reversal of the *in vitro* bacteriostatic effect of P.A.S. by P.A.B. has been described;¹⁴⁰ another author found no reversal with P.A.B., but found P.A.S. to resemble P.A.B. in itself inhibiting sulphonamide antibacterial action.¹⁴² We must guard against premature judgment here since it is clear that substances of chemical purity have seldom been available, and in the Reporter's laboratory samples of commercially available material drawn from two continents have been found to contain as little as 30% of 4-aminosalicylic acid. The clinical status of P.A.S. is as yet undefined.

In contrast to the minute concentrations of P.A.B. which inhibit sulphonyl drugs, an antibacterial action of *p*-aminobenzoic acid in high concentration is now well appreciated,¹⁴³ and of great interest is a claim that doses of 0.6 g./kg. gave protection to groups of guinea-pigs against an experimentally induced tubercle infection.¹⁴³ E. Hoggarth and A. R. Martin¹⁴⁴ tested 10 sulphones by a chemotherapeutic antituberculosis test in mice, and concluded that their previous *in vitro* tests were an unreliable guide. The same appeared to be true of a series of sulphonamides¹⁴⁵ which they also examined.

In a further trial of drugs prepared primarily as antimalarials, compounds related to 2-*p*-chloroanilino-4- δ -diethylamino- α -methylbutylamino-6-methylpyrimidine had significant chemotherapeutic effects against tubercle bacilli.¹⁶⁶ Of a further 110 related compounds examined by chemotherapeutic tests no compound was uncovered of greater activity, and the authors noted the similar requirements for chemotherapeutic activity against the malaria parasite and the tubercle bacillus.¹⁶⁷

Antibiotics.—Streptomycin¹⁴⁴ is the most effective known chemotherapeutic agent for the control of experimental tuberculosis in the experimental animal which infection it will almost completely suppress under favourable conditions.¹⁴⁵ Two biologically active streptomycins have been isolated from the product of active strains. The substance formerly known as streptomycin A, which is the major constituent, is properly called streptomycin. It is *N*-methyl-L-glucosaminidostreptosidostreptidine. The

¹³⁹ *Quart. Bull. N.W. Univ. Med. Sch.*, 1946, **20**, 420.

¹⁴⁰ G. W. Raleigh and A. S. Youmans, *J. Bact.*, 1947, **54**, 409.

¹⁴¹ H. Erlenmeyer, B. Prijs, E. Soskin, and E. Suter, *Helv. Chim. Acta*, 1948, **31**, 988.

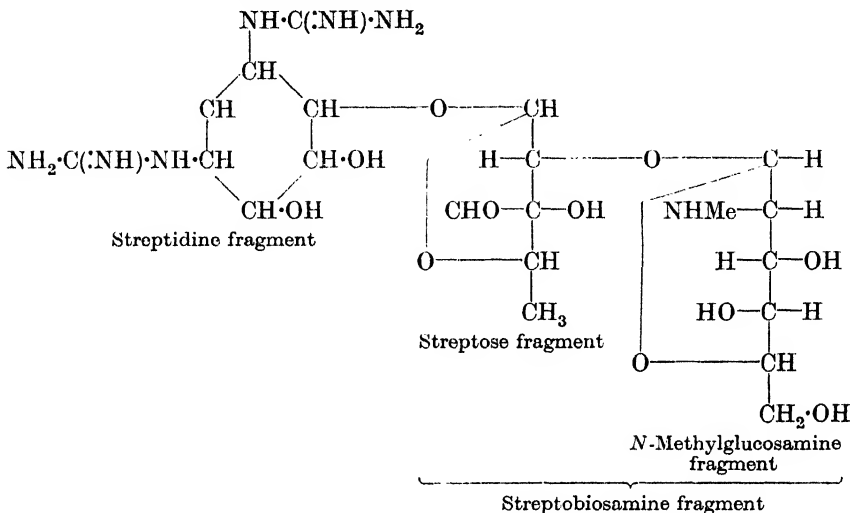
¹⁴² E. Diezfelusy, *Arkiv Kemi, Min., Geol.*, 1947, **24**, B, No. 1.

¹⁴³ M. Di Fonzo, *Farm. Sci.*, 1947, **2**, 287.

¹⁴⁴ A. Schatz, E. Bugie, and S. A. Waksman, *Proc. Soc. Exp. Biol.*, 1944, **55**, 66.

¹⁴⁵ W. H. Feldman, H. C. Hinshaw, and F. C. Mann, *Amer. Rev. Tuberc.*, 1945, **52**,

minor component is mannosidostreptomycin, formerly called streptomycin B, which is represented as D-mannosido-*N*-methyl-L-glucosaminidostreptosido-streptidine; a "streptomycin residue" is also recognised which has antibiotic and enhancement properties.¹⁴⁶ The exact structure of streptomycin (*N*-methyl-L-glucosaminidostreptosidostreptidine) of molecular formula $C_{21}H_{39}O_{12}N_7$, is unknown. Hydrolysis yields biologically inactive streptidine, $C_8H_{18}O_4N_6$, and streptobiosamine, $C_{13}H_{23}O_9N$.^{147, 148} Streptomycin has an established place in clinical tuberculosis.



Suggested formula for streptomycin.

Dihydrostreptomycin^{149, 150} prepared by catalytic reduction of streptomycin has significantly less neurotoxicity,^{151, 152} is equally effective with streptomycin in experimental tuberculosis,¹⁵³ is tolerated in patients hypersensitive to streptomycin,¹⁵⁴ and causes neurotoxicity more slowly and with higher doses than does streptomycin; ^{154, 155} moreover, it appears equally effective in man.^{154, 155}

Mode of Action.—The antibacterial action of streptomycin, but not of dihydrostreptomycin, is reversed by cysteine, hydroxylamine, and 2-amino-

¹⁴⁶ S. A. Waksman, *Science*, 1948, **107**, 233.

¹⁴⁷ E. J. Oswald and J. K. Nielsen, *ibid.*, 1947, **105**, 84.

¹⁴⁸ K. Folkers, N. C. Brink, and F. A. Kuehl, *ibid.*, 1945, **102**, 506.

¹⁴⁹ R. L. Peck, C. E. Hoffhine, and K. Folkers, *J. Amer. Chem. Soc.*, 1946, **68**, 1390.

¹⁵⁰ J. R. Bartz, J. Controulis, H. M. Crooks, and M. C. Rebstock, *ibid.*, 1946, **68**, 2163.

¹⁵¹ R. Donovan and G. Rake, *J. Bact.*, 1947, **53**, 205.

¹⁵² A. O. Edison, B. M. Frost, O. E. Graessle, J. E. Hawkins, S. Kuna, C. W. Mushett, R. H. Silbur, and M. Solotorovsky, *Amer. Rev. Tuberc.*, 1948, **58**, 487.

¹⁵³ W. H. Feldman, A. G. Karlson, and H. C. Hinshaw, *ibid.*, p. 494.

¹⁵⁴ L. B. Hobson, R. Tompsett, C. Muschenheim, and W. McDermot, *ibid.*, p. 501.

¹⁵⁵ H. C. Hinshaw, W. H. Feldman, D. T. Carr, and H. A. Brown, *ibid.*, p. 525.

ethanethiol. Inactivation by cysteine can itself be reversed by iodine in chloroform, a demonstration which proves that thiol groups are not involved. Interesting evidence that streptomycin may be involved in an unknown metabolic system arises from experiments on development of resistance.¹⁵⁶ Thus in one population were (a) sensitive, (b) insensitive, and (c) dependent organisms. The suggestion is made that streptomycin competes for the essential metabolite in (a), acts as a growth factor in (c), and is an essential metabolite synthesised by the organism in (b). The growth-promoting properties of streptomycin on dependent strains is shared by dihydrostreptomycin and by mannosidostreptomycin and its dihydro-derivative.¹⁵⁷ Urea and its purine and pyrimidine precursors, but not thiourea, antagonise the *in vitro* activity against tubercle bacilli.¹⁵⁸ An interesting reversal of streptomycin activity is that by lipositol, an inositol-galactose complex, found in association with the phosphatide fraction of brain and soya-bean, one part of which reverses 300 parts of streptomycin.¹⁵⁹

Other Chemotherapeutic Antibiotics.—Licheniformin is a polypeptide-containing antibiotic described by Callow *et al.*¹⁶⁰ It has been shown to inhibit the development of experimental tuberculosis in mice.¹⁶¹ Whether its described nephrotoxicity is intrinsic is a subject of current enquiry.

A second chemotherapeutic antibiotic, nisin, appears to have sufficiently low toxicity and sufficient high therapeutic efficiency against experimental tuberculosis in guinea-pigs to justify further development. Its chemotherapeutic activities in other fields appear imposing.^{162, 163}

Cepharanthine.—This alkaloid is claimed to be extremely effective in the treatment of tuberculosis and leprosy in man, for whom it is no more toxic than quinine. Credited with causing lysis of tubercle bacilli *in vitro*, it is said to arrest experimental tuberculosis in the guinea-pig.^{168, 169} The effect on experimental tuberculosis in the guinea-pig has not been confirmed.¹⁷⁰

Additional Various Chemotherapeutic Claims.—References have been found in the literature to claims for chemotherapeutic activity in the experi-

¹⁵⁶ F. J. Paine and M. Finland, *Science*, 1948, **107**, 143.

¹⁵⁷ G. Rake, *Proc. Soc. Exp. Biol. N.Y.*, 1948, **87**, 249.

¹⁵⁸ R. J. Fitzgerald and F. Bernheim, *J. Biol. Chem.*, 1948, **172**, 845.

¹⁵⁹ J. Rymer, G. J. Wallace, L. W. Byers, and H. E. Carter, *ibid.*, 1947, **169**, 457.

¹⁶⁰ R. K. Callow and P. D'Arcy Hart, *Nature*, 1946, **157**, 334.

¹⁶¹ R. K. Callow, R. E. Glover, P. D. Hart, and G. M. Hills, *Brit. J. Exp. Path.*, 1947, **28**, 418.

¹⁶² A. T. R. Mattick and A. Hirsch, *Lancet*, 1946, *i*, 417.

¹⁶³ *Idem*, *ibid.*, 1947, *ii*, 8.

¹⁶⁴ *Brit. J. Pharmacol. Exp. Med.*, 1948, **3**, 146.

¹⁶⁵ E. Hoggarth, A. R. Martin, and E. H. P. Young, *ibid.*, p. 153.

¹⁶⁶ E. Hoggarth and A. R. Martin, *ibid.*, p. 156.

¹⁶⁷ E. Hoggarth, A. R. Martin, M. F. C. Paige, M. Scott, and E. Young, *ibid.*, p. 160.

¹⁶⁸ Nat. Res. Coun. Lit. Survey, U.S.A., 1948.

¹⁶⁹ J. Büchi, *Schweitz. Apoth.-Ztg.*, 1945, **83**, 198.

¹⁷⁰ Report, Int. Red Cross, Geneva, *Méd. et Hyg.*, 1946, **4**, 1.

mental animal for the following various substances. The list, from which claims for sulphones and sulphoxides have been eliminated, is as follows: sodium thiosulphate,¹⁷² a 0.78% aqueous iodine solution,¹⁷³ safranine, indamine-blue, tanninheliotrope,^{174, 175} *p*-ethylaniline, *p*-chloroaniline, *p*-aminophenyl hexyl ether, ethyl *p*-aminobenzoate, 3 : 4-dichloroaniline,¹⁷⁶ 2 : 5-bis-(*p*-sulphonamidophenylamino)benzoquinone and its 3 : 6-dichloro- and diacetyl derivatives,¹⁷⁷ phloroglucinol,¹⁷⁸ formic acid,¹⁷⁹ ethyl stearate, ethyl laurate, ethyl myristate, ethyl *n*-nonanecarboxylate, ethyl arachidate, ethyl palmitate,¹⁸⁰ calciferol,¹⁸¹ ascorbic acid,¹⁸² pine oil,¹⁸³ nicotinamide,¹⁸⁴ *N*¹-3 : 4-dimethylbenzoylsulphanilamide, and thiouracil.¹⁸⁵

Empirical *in vitro* Screening.—It is a task of dubious significance to identify the possible leads indicated by the enormous total of *in vitro* experiments in which acid-fast bacilli and tubercle bacilli of various origin, known and unknown, have failed to grow in the presence of added substances. No criticism of the many admirable detailed studies of variations of activity within a chemical series, as such, should be read into these remarks; however, even here the severe limitations of *in vitro* comparisons, usually appreciated at their source, are often lost to the unsuspecting into whose hands fall the surveys of "antitubercular drugs." Nor is this all. A survey of the literature since the assessment by Wells and Long² can convey but a hint of the field covered, since every student of the subject is aware of the existence of a huge total of additional examinations made within commercial organisations. The purely negative results are seldom published. The interested reader is referred to C. O. Guss and M. C. Kloetzel's up-to-date survey of "potential tuberculo-therapeutic compounds."¹⁸⁶ However, in the following section apparently significant leads derived from *in vitro* tests will be discussed.

Naphthaquinones, John's Bacillus, and the Tubercle Bacillus.—Three pathogenic organisms, John's bacillus (*Mycobacterium paratuberculosis*), the tubercle bacillus (*Mycobact. tuberculosis* var. *hominis*), and the leprosy bacillus (*Mycobact. lepræ*), together with the non-pathogenic timothy-grass bacillus *Mycobact. phlei*, form a closely related acid-fast group.

¹⁷¹ W. H. Feldman, personal communication, 1948.

¹⁷² J. K. Yanagisawa, *Jap. J. Exp. Med.*, 1936, **14**, 395.

¹⁷³ E. W. Emmart, *Amer. Rev. Tuberc.*, 1946, **53**, 83—95.

¹⁷⁴ G. Meissner and E. Hesse, *Arch. exp. Path. Pharm.*, 1931, **159**, 676.

¹⁷⁵ E. Hesse, G. Meissner, and G. Quast, *ibid.*, 1928, **135**, 82.

¹⁷⁶ K. I. Melville and R. L. Stehle, *Canadian J. Res.*, 1944, **22**, E, 95.

¹⁷⁷ I. Y. Postovsku and Z. V. Pushkareva, *J. Gen. Chem. Russia*, 1946, **16**, 277.

¹⁷⁸ Y. Ishmaui, S. Yanagami, and M. Nishigaki, *Osaka-yishinshi*, 1935, **6**, No. 5, Japan; *Lit. Tuberc. Forsch.*, 1936, No. 5, 16.

¹⁷⁹ R. Hilgermann, *Med. Klin.*, 1939, **35**, 739.

¹⁸⁰ L. Nigre, A. Berthelot, and J. Bretey, *Compt. rend. Soc. Biol.*, 1936, **208**, 1816.

¹⁸¹ W. Raab, *Science*, 1946, **103**, 670.

¹⁸² E. Sengir, *Ankara Yukalk Zir. Institusa Deig.*, 1946, **6**, 467.

¹⁸³ E. Daizins, *Ann. Inst. Pasteur*, 1938, **61**, 172.

¹⁸⁴ V. Chorine, *Compt. rend. Soc. Biol.*, 1945, **220**, 150.

¹⁸⁵ C. J. Duca and M. M. Steinbach, *Amer. Rev. Tuberc.*, 1946, **53**, 594.

In 1911 F. W. Twort and G. L. Y. Ingram^{186, 187} demonstrated, probably for the first time for any micro-organism, a clear growth factor requirement for John's bacillus.^{186, 187} The growth factor(s) was supplied by vaccines of other acid-fast bacteria including *Mycobact. tuberculosis* var. *hominis* and *Mycobact. phlei*, and it was found that lipin solvents could extract the principle(s). Thirty years later D. W. Woolley and J. R. McCarter¹⁸⁸ found phthiocol (3-hydroxy-2-methyl-1:4-naphthaquinone) isolated from tubercle bacilli,¹⁸⁹ and synthetic 2-methyl-1:4-naphthaquinone, a biologically active vitamin-K analogue, markedly to increase growth of John's bacillus on synthetic medium, but to be inferior to concentrates extracted from *phlei* cells, so that it was clear that the *phlei* concentrates contained additional growth substances. More recently, growth-stimulating substances, whose effect could not be duplicated by vitamin K or its analogues, have been identified in bovine tuberculin, that is, the soluble products of the metabolism of the organism.¹⁹⁰ This project is being furthered at several centres.*

B. C. J. G. Knight¹⁹¹ has recently collected the evidence for those organisms which synthesise vitamin-K-active substances and notes our ignorance of whether adapted¹⁹² John's bacillus strains synthesise these substances. The importance of these observations lies in the demonstration of a vitamin-K-active substance as a product of bacterial synthesis. Thus, on the one hand is the demonstration of a vitamin-K-active substance produced by bacterial synthesis and on the other of a growth factor for John's bacillus. Is this adequate evidence that naphthaquinones have important metabolic functions in John's bacillus, and in acid-fast organisms in particular? That this may be so derives support¹⁹¹ from the demonstration by McIlwain that iodinin, a purple dye from *Chromobacterium iodinum*, inhibits the growth of a number of bacteria including streptococci and the tubercle bacillus.¹⁹³ It was further shown that 1:4-, 1:5-, and

¹⁸⁶ *Proc. Roy. Soc.*, 1911, **84**, B, 517.

¹⁸⁷ "A Monograph on John's Disease," Ballière, Tindall and Cox, London, 1913.

¹⁸⁸ *Proc. Soc. Exp. Biol. N.Y.*, 1940, **45**, 357.

¹⁸⁹ M. S. Newman, J. A. Crowder, and R. J. Anderson, *J. Biol. Chem.*, 1934, **105**, 279.

¹⁹⁰ J. Glavind and H. Dam, *Physiol. Plantarum*, 1948, **1**, 1.

¹⁹¹ "Growth Factors in Microbiology. Vitamins and Hormones. III." Academic Press, New York, 1945.

¹⁹² G. W. Dunkin, *J. Comp. Path.*, 1933, **46**, 159.

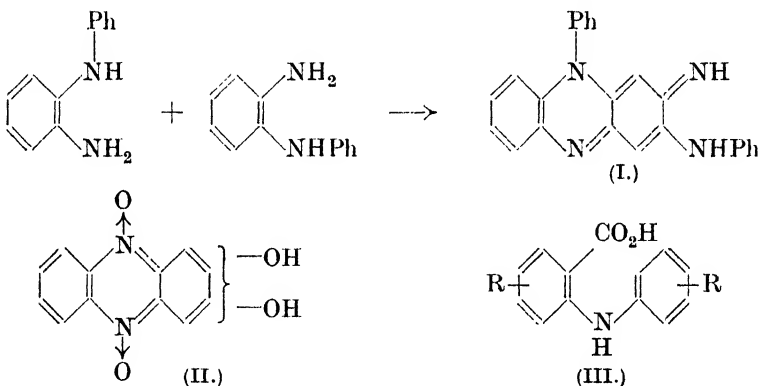
¹⁹³ H. McIlwain, *Biochem. J.*, 1943, **37**, 265.

* *Added in Proof*.—There has been a tendency to relate Woolley and McCarter's observations¹⁸⁸ to the emergence of adapted strains since few workers have been able to duplicate the results. J. Francis, J. Madinaveitia, H. M. MacTurk, and G. A. Snow (*Nature*, 1949, **163**, 365) failed to detect free phthiocol in fresh extracts of *Mycobacterium tuberculosis* but isolated a new vitamin-K-like yellow oil of molecular weight greater than that of vitamin K₁. This oil gave phthiocol on alkaline hydrolysis. Neither the oil nor phthiocol was a growth-factor for John's bacillus.

The latter authors report the isolation, from *Mycobact. phlei*, of a growth-factor for John's bacillus obtained crystalline as a colourless aluminium derivative of approximate formula, C₁₉H₁₅O₁₀N₂Al; it is apparently not a naphthaquinone.

1:8-dihydroxyanthraquinones and 2-methyl-1:4-naphthaquinone were active in reversing the inhibitory action of iodinin.

A number of authors have found inhibitors modelled on vitamin-K-active naphthaquinones to inhibit the growth of tubercle bacilli in the test tube,^{194, 195, 196} but these and similar analogues have proved inactive in the experimental animal.¹⁹⁴ Whether the normal vitamin-K concentration of the experimental animal (guinea-pig) is too high to allow the maintenance of a ratio of the antibacterial substance to its inhibitors (vitamin K) or whether the bacteriostatic substance is degraded in the body has not been proved. The former possibility is of special interest since it will be recalled that pantoyletaurine, the sulphonic acid analogue of pantothenic acid, can retain its bacteriostatic activity *in vivo* and thus behave as a chemotherapeutic agent in one animal but not in the other. The normal pantothenate concentration in the blood of mice is higher than in rats, so that a chemotherapeutic ratio of pantoyletaurine: pantothenate could be maintained in the latter but not in the former.¹⁹⁷ V. C. Barry, J. G. Belton, M. L. Conalty, and D. Twomey²⁰⁰ found the dark red base, $C_{24}H_{18}N_4$ (I), produced by oxidation and condensation from 2-aminodiphenylamine to be powerfully antiseptic in the case of the tubercle bacillus. Its high toxicity precluded



its use for animal protection experiments. The chemical relation to iodinin (II) is of interest. Whether the specific *in vitro* activity of the diphenylamine-2-carboxylic acid derivatives (III) recently described are also related to naphthaquinone metabolism has not been shown.²⁰¹

A naturally occurring quinone of similar structure to iodinin is usnic acid. Of potent activity *in vitro* against the tubercle bacillus,^{198, 199} it does not appear to have been tested in the animal.

¹⁹⁴ W. Alcalay, *Schweiz. Z. Path.*, 1947, **10**, 229.

¹⁹⁵ C. N. Iland, *Nature*, 1948, **161**, 1010.

¹⁹⁶ A. Gronwall and B. Zetterberg, *Uppsala Läkarefören Förh.*, 1947, **52**, 199.

¹⁹⁷ H. McIlwain and F. Hawkins, *Lancet*, 1943, **i**, 449.

¹⁹⁸ V. C. Barry, L. O'Rourke, and D. Twomey, *Nature*, 1947, **160**, 800.

¹⁹⁹ F. Bustinza and A. C. Lopez, "Antibiotics from Lichens," *An. Jardin Bot. id.*, 1946, **7**, 1-38.

Inositol, Streptomycin, and Lipositol.—Inositol occurs naturally in high concentration in brain and heart muscle of higher animals; it is an essential growth factor for a fungus, *Nematospora gossypii*,²⁰² a metabolite associated with bios I of yeasts,²⁰³ and a nutritional factor associated with alopecia in a strain of mice,²⁰⁴ but it is not at present known as a nutritional requirement for any bacteria.¹⁹¹ A diverse range of bacteria synthesise inositol, including some associated with intestinal biosynthesis,¹⁹¹ as do also acid-fast organisms like the tubercle bacillus of human, bovine, and avian origin, the timothy-grass bacillus, and the leprosy bacillus (Table II). An interesting difference is seen between the inositol content of Gram-negative (and ? Gram-positive) organisms which contain from 0.09 to 0.17% and the tubercle bacillus which synthesises from 3 to 9% of inositol. Anderson and his colleagues³ found inositol among the cleavage products of the phosphatides in which it fulfilled the function of the nitrogen-containing complexes of the more usual phosphatides of higher plants and animals. By alkaline saponification of the phosphatide he isolated "maninositose" of which the cleavage products were mannose and inositol. A reference to the known cleavage products of streptomycin discussed earlier in this Report shows that streptidine may be regarded as a substituted inositol linked, it is thought, through an ether linkage to a novel sugar. A third interesting finding, which appears to relate the three observations, is the demonstration that lipositol from brain and soya bean competitively inhibits the anti-bacterial Gram-negative action of streptomycin. Lipositol from soya bean was so active that one part inhibited 300 parts of streptomycin. In 1942 J. Folch and D. W. Woolley²⁰⁵ showed brain phosphatide to contain inositol, and subsequently the inositol-containing component to which the name lipositol was given was found to have an inositol-galactose (?) structure.²⁰⁶

Enquiry directed to the isolation from virulent tubercle bacilli of inositol-containing substances with a view to a comparison of their capacity to inhibit streptomycin, when compared with lipositol, would be valuable. It would also be of interest to relate strains of tubercle bacilli sensitive or resistant to, and dependent on, streptomycin to their (inositol-containing) inhibitory substances. Meantime the direct empiric lead might be followed.

Calciferol and Lupus.—It was first observed clinically that cutaneous tuberculosis responded to the oral administration of calciferol (vitamin D₂).^{207, 208} A suppressive effect upon experimental tuberculosis in guinea-pigs is claimed²⁰⁹ with an additional observation that "inactivated" ergosterol, in larger doses, gave a superior effect. It is clearly desirable to

²⁰⁰ *Nature*, 1948, **162**, 622.

²⁰¹ A. A. Goldberg, H. S. Jefferies, and H. S. Turner, *Quart. J. Pharm.*, 1948, **21**, 10.

²⁰² H. W. Buston and B. N. Pramanik, *Biochem. J.*, 1931, **25**, 1656, 1671.

²⁰³ E. V. Eastcott, *J. Physiol.*, 1928, **32**, 1094.

²⁰⁴ D. W. Woolley, *J. Biol. Chem.*, 1941, **139**, 29.

²⁰⁵ *Ibid.*, 1942, **142**, 963.

²⁰⁶ D. W. Woolley, *ibid.*, 1943, **147**, 481.

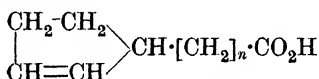
²⁰⁷ G. B. Dowling and E. W. P. Thomas, *Proc. Roy. Soc. Med.*, 1945, **39**, 96.

²⁰⁸ A. Charpy, *Ann. Dermat. France*, July, 1945.

²⁰⁹ W. Raab, *Science*, 1947, **106**, 546.

attempt to identify the active substance in man and in the animal, and a study of excretory products might be expected to throw light on the problem. In another connection it has been found that feeding the allied molecule cholesterol to rats resulted in the excretion of fatty acids of molecular formula $C_{25}H_{50}O_2$,²¹⁰ and Sir Robert Robinson has indicated the possible route of degradation which would involve unwinding the tetracyclic nucleus of the steroid by breaks at the point where the rings are fused, and also at some peripheral point, and in the side chain, and he also indicated a possible degradation to 5:18-dimethyltricosanoic acid. Should the acid obtained by feeding cholesterol prove to be a branched-chain acid, the determination of its structure is a matter of some urgency, and a comparison with the excretory products derived from feeding calciferol and "inactivated" ergosterol most desirable.

Leprosy and Chaulmoogra.—The hint supplied by the traditional use of chaulmoogra oil in leprosy in the East was followed up by Power and his colleagues^{216, 217} and culminated in the elucidation of the structure of chaulmoogric and hydrocarpic acids.^{211, 216, 217}



(Chaulmoogric acid, $n = 12$.)

Hydnocarpic acid, $n = 10$.)

A large number of di-substituted acetic acids were synthesised and tested *in vitro*. ω -cycloHexyl-substituted aliphatic acids had maximum *in vitro* activity with 14—17 carbon atoms, and activity was greatest when the carboxyl group was in the centre of the chain. A further series of dialkylacetic acids without a ring structure was also studied. These active long-chain acids were too irritant to test on experimental animals.²¹¹

Starting from roccellic acid (α -methyl- α' - n -dodecylsuccinic acid) Barry and his colleagues²¹² similarly encountered maximum *in vitro* activity against tubercle bacilli, at a chain-length of 13—15 carbon atoms. A half-ester of $\alpha\alpha'$ -di- n -heptylsuccinic acid, differing from heptyloctylacetic acid only in the possession of an extra carbethoxy-group, was found to be 10 times as active *in vitro*. These compounds were inhibited by serum and displayed little *in vivo* activity, but may prove of value when used by local application.²¹³ There has been an unconfirmed claim that the ethyl esters of chaulmoogric acids are synergic with streptomycin and may have a use in renal tuberculosis.²¹⁴ Streptomycin appears to have little clinical curative effect in leprosy.²¹⁵

²¹⁰ R. P. Cook, N. Polgar, and R. O. Thompson, *Biochem. J.*, 1948, **43**, ix.

²¹¹ W. M. Stanley, G. H. Coleman, C. M. Greer, J. Sacks, and R. Adams, *J. Pharmacol.*, 1932, **45**, 121.

²¹² V. C. Barry, *Nature*, 1946, **158**, 863.

²¹³ V. C. Barry, personal communication, 1948.

²¹⁴ G. E. Slotkin and S. Wilber, *Int. J. Leprosy*, 1948, **16**, 273.

²¹⁵ G. H. Faget and P. T. Erickson, *J. Amer. Med. Assoc.*, 1948, **136**, 451.

²¹⁶ F. B. Power and F. H. Gornall, *J.*, 1904, **85**, 851.

²¹⁷ M. Barrowcliff and F. B. Power, *J.*, 1907, **91**, 557.

Epilogue.

“ ‘It is a poor sort of memory that only works backwards,’ the Queen remarked.”—Lewis Carroll.

The discussion of material presented in this Report derives its impetus from knowledge about the chemical attack upon the tubercle bacillus secured mainly during the last ten years. The chemotherapeutic success in the field of allied bacterial disease which Wells and Long prophetically expected to stimulate the more difficult attack on the tubercle bacillus has proved effective. We may confidently expect more effective antibiotic agents to be discovered, and more effective chemotherapeutic agents to be synthesised ; in objective the empirical approach has become routine : only the methods differ.

The object of the direct approach to the chemotherapy of tuberculosis may be simply stated as “the elimination of the parasite.” We have to consider the possibility that this simplification may falsify the clinical status, by reason of the morbid anatomy of the disease to which attention has been drawn. A second weighty consideration is the slow metabolism of the causal parasite which endows it with a marked capacity to survive unfavourable environments. Emphasis has been placed, therefore, upon those pathological characteristics which make tuberculosis a special problem.

The indirect approaches which have been indicated derive their sources from the purposeful studies of the biochemical lesions caused by the chemical components of the organism, lipins, carbohydrates, and proteins. In this connection the ingenuity of the organic chemist can be exploited to prepare synthetic, physiologically active analogues of the causal agents, to model related physiologically “blocking” structures to them, and to couple these new presumed haptens with known antigenic proteins. Emphasis must also be placed on discovering the physiological functions of the presumed essential metabolites. The protein component(s) does not appear to have attracted the attention it may deserve, since the evidence appears complete that this substance is directly responsible for a host-parasite collaboration which results in hypersensitisation and death of the host's tissue cells. A chemical attack related, for the purpose of illustration only, to the toxin-antitoxin mechanisms appears worthy of chemical attention.

But these are words, and a poor substitute for experimental evidence.

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R. BENTLEY.

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A. J. P. MARTIN.

C. RIMINGTON.

F. SANGER.

ANALYTICAL CHEMISTRY.

1. INTRODUCTION.

THE demand for increased production of goods and materials—and for increased rate of production—created by war-time exigencies and intensified by post-war plans for economic recovery have done much to accelerate the natural development of analytical methods that are both rapid and accurate, yet suitable for routine measurements by semi-skilled or hastily trained operatives. Nowhere does this appear so clearly as in the field of emission spectrography where a remarkable degree of mechanisation has already been achieved. The special interests of soil-scientists and biochemists have likewise speeded the developments of the Lundegårdh technique foreshadowed in the Report for 1941 and now described in the section of flame photometry.

Yet despite the ever-increasing importance of physical methods, more than half the papers published annually still relate to the procedures of volumetric analysis, and although there have been no spectacular developments the past decade has seen steady progress in its techniques and applications, some of which are reviewed in Section 4 of this Report. The last section deals with a complex naturally occurring material of great economic importance—sea water—which presents many absorbing and difficult problems to the analyst.

H. I.

2. ANALYTICAL EMISSION SPECTROGRAPHY.

The value of emission spectrography as an analytical technique was thoroughly established when the subject was last reviewed¹ but its study received a major impetus at the outbreak of war in 1939, when industry was faced with rapid expansion. In the metallurgical industries, and particularly in those concerned with light alloys, the provision of increased analytical facilities presented serious difficulties since the additional skilled staff and buildings needed for chemical methods of analysis were rarely available. The problem was happily solved by the installation of spectrographic equipment which provided analyses of a satisfactory degree of accuracy in a fraction of the time taken by the chemical methods then in use, whilst it was economical in both laboratory space, and numbers and quality of personnel. From that time progress has been continuous.

The process employed in quantitative analytical spectrography is treated at length in the standard textbooks² and various specific techniques have

¹ *Ann. Reports*, 1937, **34**, 454.

² W. R. Brode, "Chemical Spectroscopy," John Wiley & Sons Inc., New York, and Chapman and Hall Ltd., London; F. Twyman, "The Spectrochemical Analysis of Metals and Alloys," Charles Griffin & Co. Ltd., London; D. M. Smith, "Collected Papers on Metallurgical Analysis by the Spectrograph," The British Non-Ferrous Metals Research Association, London; "Analysis of Aluminium and its Alloys: Spectrographic and Polarographic Analysis," The British Aluminium Co. Ltd.

been described in the literature.³ When spectrography is used as an analytical tool in industry the details of the method employed depend largely on the nature of the material to be analysed, the speed and accuracy required, and the equipment available, but the following steps are common to most procedures. The material is first sampled, either by taking it into solution in a suitable solvent, by pelleting, or by casting it into the form of rods or discs which can form one or both of the electrodes of the excitation discharge. After being sampled, the material is suitably excited, the spectrum is recorded photographically and the densities of the spectrum line images are measured by means of a microphotometer. Subsequent calculations allow the concentrations of the constituents of the sample to be deduced from these density measurements.

Errors in the conventional method of quantitative analysis may arise at all stages.⁴ Inefficient sampling is an obvious source of inaccuracy but one that can be readily minimised. The numerous errors associated with the excitation⁵ of the spectrum and the use of the photographic plate are less obvious and are more difficult to overcome.

It is generally accepted that attempts to accelerate the spectrographic process by shortening the exposure time and by using fast photographic emulsions may have a deleterious effect on the overall accuracy of the analysis, and it is better to increase the accuracy of the method and to gain speed by reducing the number of replicate analyses carried out on each sample.

The accuracy of analysis has been the subject of considerable attention,⁶ and after an improvement brought about by a proper understanding of the photographic process and the requirements of accurate photometry, attention was directed at improving the spark source normally employed for the routine analysis of metallic materials. Several types of improved excitation unit have been described, and their use may, in general, be said to result in an improvement in analytical accuracy of some 50% when they are applied to light alloys; with ferrous materials the improvement

³ S. Levy, *J. Appl. Physics*, 1940, **11**, 480; J. van Calker, *Spectrochim. Acta*, 1944, **2**, 333; P. Cohen, *J. Opt. Soc. Amer.*, 1946, **36**, 489; A. Walsh, "Collected Papers on Metallurgical Analysis by the Spectrograph" (see ref. 2), p. 65; A. Cornu, *Compt. rend.*, 1946, **222**, 1341; J. Wilken, *Metallwirts.*, 1940, **19**, 121; A. von Zeerleder and F. Rohner, *Helv. Chim. Acta*, 1940, **23**, 1287; H. Correll, *Aluminium*, 1940, **22**, 525; R. W. Callon and J. E. Burgener, *J. Opt. Soc. Amer.*, 1944, **34**, 543; H. L. Collins and R. W. Callon, *Canad. Metals*, 1945, **8**, 20; G. S. Smith, *Met. Ind.*, 1945, **67**, 226; 1947, **70**, 23; "Reports of A.S.T.M. Committee E-2 on Spectrographic Analysis," *Proc. Amer. Soc. Test. Mat.*, 1939 onwards.

⁴ T. A. Wright, *Amer. Soc. Test. Mat.*, Reprint No. 112, 1940; H. Mäder and R. Poetzelberger, *Metallwirts.*, 1940, **19**, 381; N. V. Buyanov, *Zavod. Lab.*, 1940, **9**, 69; V. K. Prokof'ev, *Izvest. Akad. Nauk, S.S.S.R.*, 1940, (*Phys.*), **4**, 5; A. G. Quarrell and G. E. A. Bramley, *J. Inst. Metals*, 1941, **67**, 25; W. Seith and H. Hessling, *Z. Elektrochem.*, 1943, **49**, (4/5), 210; S. Levy and O. W. Christine, *J. Opt. Soc. Amer.*, 1946, **36**, 503.

⁵ H. Mäder and R. Poetzelberger, *Spectrochim. Acta*, 1939, **1**, 213.

⁶ A. E. Ruehle, *Bull. Amer. Soc. Test. Mat.*, 1941, **33**; H. B. Vincent and R. A. Sawyer, *J. Opt. Soc. Amer.*, 1942, **32**, 686.

is less marked but is still appreciable. Microphotometry of the photographic negative, the introduction of which had enabled consistently satisfactory analyses to be carried out by relatively unskilled operators, involves minor but appreciable errors. Recent developments aim to supplant it by the direct photoelectric measurement of the spectrum line intensities.

The speed of analysis has continuously increased, and it is commonplace to find methods using photography of the spectrum and subsequent microphotometry of the line images which take no more than 10—15 minutes for a complete analysis of a sample for several elements, whilst if a direct photoelectric measurement of line intensity is made the time may be no more than 2 minutes.

The spectrograph has also been applied to an ever-increasing range of analyses outside the metallurgical field and is now widely used in such diverse work as the analysis of biological materials, ores, and oil additives.

Progress in the past ten years may thus be summed up as an increase in the accuracy, speed, and scope of the method. The more recent developments in source units coupled with the application of multiplier photocells to the direct measurement of spectrum line intensities show promise of producing still greater accuracy and speed in the near future.

Personal Errors.—The spectrographic process involves numerous steps, and many of them are liable to introduce errors when they are carried out by inexperienced workers. Attention has therefore been directed at simplifying and mechanising the process so that it is as independent as possible of the mistakes and judgment of the operator.

In preparing the electrodes for excitation, manual filing has been largely replaced by machining or grinding, and the machines designed for this operation provide an electrode tip of standardised shape and finish.⁷ Improved electrode stands have been described⁸ and in the type due to A. von Zeerleder and F. Rohner⁹ three pairs of electrodes are accommodated; the first pair is automatically pre-burned for a given period, the second provides the spectrum lines in analysis, and the third can be simultaneously changed for a further pair of fresh electrodes. The photographic exposure has been controlled by the use of automatic timing switches which give an exposure of predetermined duration¹⁰ or by photoelectric devices which expose the photographic emulsion until a fixed amount of light energy has been emitted by the discharge.¹¹ Automatic photographic processing as

⁷ C. L. Waring, *Metals and Alloys*, 1945, **21**, 1013; H. Moritz, *Aluminium*, 1940, **22**, 421; H. Kaiser, *Spectrochim. Acta*, 1942, **2**, 288; E. J. Eastmond, *J. Opt. Soc. Amer.*, 1944, **34**, 621; K. R. Mayors and T. H. Hopher, *Ind. Eng. Chem. Anal.*, 1941, **13**, 647.

⁸ H. R. Clayton, *J. Sci. Instr.*, 1941, **18**, 65; B. F. Scribner and C. M. Carless, *J. Res. Nat. Bur. Stand.*, 1943, **80**, 41; *J. Opt. Soc. Amer.*, 1943, **33**, 515; W. D. Owsley and R. C. McReynolds, *Rev. Sci. Instr.*, 1942, **13**, 342.

⁹ *Spectrochim. Acta*, 1940, **1**, 400.

¹⁰ G. Balz and G. Reiniger, *ibid.*, p. 323; F. Walbank, *ibid.*, 1941, **2**, 150; R. H. Keck, *ibid.*, 1944, **2**, 389.

¹¹ J. S. Sedov, *Compt. rend. (Doklady) Acad. Sci. U.S.S.R.*, 1943, **41**, 329; H. R. Clayton, *J. Sci. Instr.*, 1946, **23**, 233.

used for large-scale roll-film development has not been applied to spectrography, but commercial equipment of a semi-automatic nature for developing, fixing, washing, and drying is available.¹² Many types of microphotometer have been devised,¹³ ranging from models designed for very rapid working¹⁴ to those which are prepared to sacrifice speed to the attainment of a higher accuracy.¹⁵ In this country the Hilger non-recording microphotometer is almost universally employed, partly for preference and partly because it is the only suitable instrument manufactured here. It is a basically simple apparatus requiring little or no maintenance and is convenient to use, but it is considered by some users to compare unfavourably with representative Continental and American instruments because of the slow speed of response of its galvanometer and its critically focussed optical system.

The calculation of the analytical results from the microphotometric measurements has been accelerated and simplified by the use of calculators which convert the readings of the microphotometer galvanometer into relative light intensity values and subsequently concentrations of the various minor constituents.¹⁶ These instruments have become almost a necessity in those laboratories where large numbers of determinations are made and various patterns have been described. Three interesting detailed descriptions of accessory equipment of the type mentioned above have been published by H. Brackebusch,¹⁷ J. L. Saunderson and V. J. Caldecourt,¹⁸ and H. Moritz.¹⁹

Sampling.—To avoid heterogeneity in the sample, many workers have been attracted by methods of analysis involving the use of a solution of the material under test.²⁰ This procedure has several advantages; non-metallic and non-conducting materials can be satisfactorily dealt with, and

¹² See, e.g., trade literature of Associated Research Laboratories, Glendale, California.

¹³ R. C. Machler, Proc. 7th Summer Conf. on Spec. and its Applications, Mass. Inst. Tech., 1939, 1940, 65; E. M. Thorndike, *Ind. Eng. Chem. Anal.*, 1941, **13**, 66; A. Gatterer, *Spectrochim. Acta*, 1941, **1**, 352; H. B. Vincent and R. A. Sawyer, *J. Opt. Soc. Amer.*, 1941, **31**, 639; W. S. Baird, *ibid.*, p. 179; H. W. Dietert and J. Schuch, *ibid.*, p. 54; R. Poetzelberger, *Spectrochim. Acta*, 1943, **2**, 296.

¹⁴ W. A. Kerr, Proc. 7th Summer Conf. on Spec. and its Applications, Mass. Inst. Tech., 1939—1940, 68; R. Fürth, *Nature*, 1942, **149**, 73; E. M. Thorndike, *Ind. Eng. Chem. Anal.*, 1941, **13**, 66—67.

¹⁵ G. O. Langstroth, K. B. Newbound, and W. W. Brown, *Canad. J. Res.*, 1941, **A**, **19**, 103.

¹⁶ G. Balz, *Aluminium*, 1940, **22**, 343; C. King, *J. Opt. Soc. Amer.*, 1942, **32**, 112; N. S. Brommelle and H. R. Clayton, *J. Soc. Chem. Ind.*, 1944, **63**, 83; D. A. Sinclair, *J. Opt. Soc. Amer.*, 1944, **34**, 689; A. P. Vanselow and G. F. Liebig, *ibid.*, p. 219; J. C. Henderson-Hamilton and A. Lourie, *J. Soc. Chem. Ind.*, 1945, **64**, 309.

¹⁷ *Spectrochim. Acta*, 1941, **2**, 18.

¹⁸ *J. Opt. Soc. Amer.*, 1944, **34**, 116.

¹⁹ *Aluminium*, 1942, **24**, 394.

²⁰ R. Bauer, *ibid.*, 1940, **22**, 9; W. D. Treadwell and R. Walti, *Helv. Chim. Acta*, 1940, **23**, 1446; A. Beerwald and W. Brauer, *Z. Metallk.*, 1941, **83**, 44; R. Walti, *Diss. Eidg. Tech. Hochsch.*, Zurich, 1943; R. J. Kiers and D. T. Englis, *Ind. Eng. Chem. Anal.*, 1940, **12**, 275.

the preparation of standards of comparison is greatly facilitated since they may be synthesised from pure salts. Excitation may be by arc, by spark, or by a controlled flame. In use, solution methods are generally more time-consuming than those employing solid electrodes of the material to be analysed, and if the solution is used as such, without evaporation, the spray from the discharge may damage other apparatus in the laboratory. Pelleting or briquetting of metallic filings²¹ or non-metallic powders²² has been used to minimise the heterogeneity of the sample but the technique is not widespread. The most generally accepted procedure for the analysis of metals is to employ electrodes of the material under test, and in the field of metallurgical analysis these are usually prepared by casting in one or two forms. If the samples are cast as rods²³ the discharge may be passed between two of them; if they are cast in disc form the discharge is made to take place between the surface of the disc and a counter electrode of another material, usually a pointed rod of graphite.²⁴ In using electrodes of these types attention must be paid to the casting technique.²⁵ The moulds employed are generally designed to give rapid chilling in order that the grain size of the metal comprising the sample shall be as fine as possible. The temperature of both the mould and the metal before sampling is usually well defined. Such measures ensure a consistently high standard of sampling, but in order to reduce further the effects of heterogeneity in the sample itself it is customary to make replicate photographic records of the spectrum of each sample, a different part of the sample being used for each exposure.²⁶ Rotating electrodes and discs have been tested to minimise sampling errors but are not generally accepted as necessary.

Calibration and Photographic Procedures.—For many years quantitative analysis was carried out almost exclusively by B. A. Lomakin's method,²⁷ in which the photographic plate is calibrated by the inclusion of spectra of standard alloys of which the composition has been determined by careful chemical analysis. This procedure suffers from two disadvantages: it is wasteful, since much of the space on the photographic plate is taken up by the spectra of the standard alloys, and the casting and analysis of the large numbers of these standards which are required for a full and useful application of the method are laborious tasks. Other methods of plate calibration have therefore been developed.

In general, these methods involve the inclusion on each photographic plate of an intensity pattern consisting of steps of known relative intensities, formed, for example, by exposing a portion of the plate to a light source

²¹ H. C. Harrison and C. C. Ralph, *Ind. Eng. Chem. Anal.*, 1943, **15**, 466; C. J. Neuhaus, *J. Opt. Soc. Amer.*, 1943, **33**, 167; P. A. Leichtle, *ibid.*, 1944, **34**, 454; H. W. Dietert, *ibid.*, 1941, **31**, 693.

²² E. J. Fitz and W. M. Murray, *Ind. Eng. Chem. Anal.*, 1945, **17**, 145; S. H. Wilson and M. Fieldes, *New Zealand J. Sci. Techn.*, 1941, **23**, 47B.

²³ H. Moritz, *Aluminium*, 1940, **22**, 421; 1943, **25**, 389.

²⁴ H. V. Churchill and J. R. Churchill, *J. Opt. Soc. Amer.*, 1941, **31**, 611.

²⁵ "Analysis of Aluminium, etc." (see ref. 2), 2nd edn., p. 16.

²⁶ *Ibid.*, p. 19.

²⁷ *Z. anorg. Chem.*, 1930, **187**, 75.

through a stepped optical wedge or rotating stepped sector. After measurement of the density of the photographic images of the steps, the characteristic curve of the photographic plate may be constructed, an artificial origin being employed because the absolute intensity of the calibrating intensity pattern is unknown. From this curve the intensity ratio of any spectrum line pair may be determined from the difference in densities of the two lines, and since the intensity ratio is a function of the concentration of the minor constituent, the amount of minor constituent present may be determined. Preliminary work is involved in finding the relationship between the intensity ratio of the two spectrum lines and the concentration of the minor constituent, but this is easily and accurately done by using analysed standards.

A method of plate calibration of this type is now commonly employed in laboratories dealing with large numbers of similar samples, but where a variety of materials are analysed the method is not so useful because of the large amount of preliminary calibration required. A proper understanding of the photographic process, as it affects photometric photometry, is essential for the successful application of plate calibration techniques to spectrography and the subject has been fully discussed by E. H. Amstein.²⁸ The photographic emulsion even on a single plate does not necessarily behave as if it were uniform in its reaction to light, whilst the image after development often lacks uniformity through an incorrect processing technique which must be carefully established and standardised. The characteristics of photographic emulsions to ultra-violet radiation have been determined²⁹ and by reference to these data workers have been able to select the most suitable type of plate and spectrum lines for their particular needs.

Correction for spectrum "background" has been considered from a photographic aspect and is usually allowed for in trace analysis,³⁰ but its effect is inappreciable in the analyses of constituents present in higher concentrations.

Excitation Sources.—Probably the most outstanding contribution to improving the speed and accuracy of the spectrographic process during the past ten years has been the development of improved excitation units to replace the D.C. arc and the condensed spark units previously employed. The condensed spark is not an ideal source for spectral excitation, particularly for those metals whose oxides are good insulators, since the amount of energy passing through the analytical gap at each individual spark is determined by the voltage at which the gap breaks down. This breakdown voltage may vary between wide limits depending on the condition of the electrode tips and the degree of ionisation of the vapour between them at the instant when the discharge starts. With gap conditions which do not

²⁸ *J. Soc. Chem. Ind.*, 1943, **62**, 51; A. C. Coates and E. H. Amstein, *ibid.*, 1942, **61**, 21.

²⁹ E. H. Amstein, *ibid.*, 1944, **63**, 172.

³⁰ L. W. Strock, *J. Opt. Soc. Amer.*, 1942, **32**, 103; R. O. Scott, *J. Soc. Chem. Ind.*, 1944, **63**, 25; J. Cholak and R. V. Story, *J. Opt. Soc. Amer.*, 1941, **31**, 730.

provide a constant breakdown value, therefore, the discharge is not reproducible. In order to stabilise the breakdown potential it is common practice to irradiate the gap with ultra-violet radiation of short wave-length, or to provide a "leading point" across the spark gap to produce a corona discharge before the passage of the spark.³¹ These methods are not entirely satisfactory and other methods of controlling the discharge have been investigated.

The first controlled condensed spark was described by O. Feussner,³² who employed a synchronous rotary spark gap to apply the discharge voltage to the gap at predetermined intervals. More recently, J. T. M. Malpica and T. M. Berry³³ have developed an electronically-controlled condensed spark in which the control is on the primary side of the high-voltage transformer. In order to define the discharge conditions more accurately, other workers have attempted to separate the high-current-density spark phase associated with the initial breakdown of the gap from a subsequent low-current-density arc phase which provides most of the light output from the discharge, but itself plays no part in gap breakdown. The first circuit of this type was developed by K. Pfeilsticker,³⁴ and subsequently, improved sources working on the same basic principles have been described by other workers. Each of these sources has its own particular merits and disadvantages; for instance, that due to A. Walsh³⁵ is so designed that it is easily constructed from readily available components, and several circuits to this design are in operation in this country with satisfactory results. The source unit described by C. Braudo and H. R. Clayton,³⁶ and produced in this country by the Metropolitan Vickers Electrical Co. Ltd., is more complicated, but dispenses with auxiliary spark gaps or synchronous interrupters by adopting electronic methods of synchronising. The "Multi-source" of M. F. Hasler and H. W. Dietert³⁷ and the circuit due to V. J. Caldecourt and J. L. Saunderson³⁸ are commercially available in America, where their versatility and stability have proved to be of great value in analytical work.

In the composite discharge units mentioned above, the analytical gap is first bridged by a very high-voltage discharge of low power and short duration. The voltage is applied to the analytical gap at a predetermined time and its value is so high that breakdown of the gap occurs practically instantaneously irrespective of the condition of the electrode tips or of the state of the vapour between them. Once the gap has been bridged, a secondary discharge at a comparatively low voltage (250—2000 v.) is allowed to cross it, and the main spectral emission is due to this discharge. Conditions in this low-voltage discharge circuit may be modified by alter-

³¹ G. Balz, H. Kaiser, and P. H. Keck, *Spectrochim. Acta*, 1941, **2**, 92; G. Balz, *Aluminium*, 1944, **26**, 60.

³² *Z. techn. Physik*, 1932, **13**, 573; *Z. Metallk.*, 1933, **25**, 73.

³³ *Gen. Elec. Rev.*, 1940, **43**, 333.

³⁴ *Z. Electrochem.*, 1937, **43**, 719; 1938, **30**, 211; 1941, **33**, 267.

³⁵ *Met. Ind.*, **66**, 243, 268, 295.

³⁷ *J. Opt. Soc. Amer.*, 1943, **33**, 218.

³⁶ *J. Soc. Chem. Ind.*, 1947, **66**, 259.

³⁸ *Ibid.*, 1946, **66**, 99.

ation of the electrical parameters to produce any type of excitation ranging from a high-current, short duration spark to an arc of long duration. The excitation conditions can thus be adjusted to suit any particular problem.

Minor constituents present in concentrations up to some 5% can be effectively dealt with by these source units and an accuracy of some $2\frac{1}{2}\%$ of the amount of minor impurity present is generally attainable on single analyses. This performance is a marked advance in light alloy analysis, but does not show a great improvement over the performance of the condensed spark for steel analysis. Coupled with the versatility of the units, however, the increase in accuracy is a very valuable attribute.

Direct Measurement of Spectrum Line Intensities.—The conditions in the electrical discharge having been stabilised, attention was directed to eliminating the photographic plate and its subsequent microphotometry.

During recent years the measurement of the low light intensities encountered in emission spectrography has been made practicable by the development of stable photo-electron multipliers.³⁹ Interest in this field has been largely centred on the electrostatically focussed multiplier photocells originally developed in America and now manufactured in this country. The characteristics of these cells are described in the makers' literature⁴⁰ and have also been studied in detail by K. G. Kessler and R. A. Wolfe⁴¹ and R. W. Engstrom.⁴² In America, where the cells were available some years ago, the direct measurement of the intensity of lines in the emission spectrum has been carried out in numerous laboratories,⁴³ and with the development of ultra-violet transparent envelopes this method has now become established and commercial direct-reading spectrographs are marketed by at least two scientific instrument manufacturers.⁴⁴

These instruments allow direct measurement of the intensities of up to 16 predetermined spectrum lines, and hence, as one line is employed as an internal standard, the determination of the concentration of 15 minor constituents can be carried out.⁴⁵ There seems little doubt that this method of spectrographic analysis is still in its infancy, but even so it shows many valuable advantages over the more orthodox procedures employing photo-

³⁹ J. A. Rajchman and R. L. Snyder, *Electronics*, 1940, **13**, 20; K. Zworykin and J. A. Rajchman, *Proc. I.R.E.*, 1939, **27**, 558.

⁴⁰ R.C.A. Manufacturing Co. Inc., Harrison, N. J.; Cosmos Manufacturing Co. Ltd., Brimsdown, Middlesex.

⁴¹ *J. Opt. Soc. Amer.*, 1947, **37**, 33.

⁴² *Ibid.*, p. 420.

⁴³ D. H. Rank, R. J. Pfister, and P. D. Coleman, *ibid.*, 1942, **32**, 390; D. H. Rank, R. J. Pfister, and H. H. Grimm, *ibid.*, 1943, **33**, 31; E. A. Boettner and G. P. Brewington, *ibid.*, 1944, **34**, 6; G. A. Nahstoll and F. R. Bryan, *ibid.*, 1945, **35**, 646; M. F. Hasler and H. W. Dietert, *ibid.*, 1944, **34**, 751; M. F. Hasler, J. W. Kemp, and H. W. Dietert, *A.S.T.M. Bull.*, 1946, No. 139, 22; J. L. Saunderson, V. J. Caldecourt, and E. W. Peterson, *J. Opt. Soc. Amer.*, 1945, **35**, 681; G. H. Dicke and H. M. Crosswhite, *ibid.*, p. 471; J. L. Saunderson and T. M. Hess, *Metal Progress*, 1946, **49**, 947.

⁴⁴ Applied Research Laboratories, Glendale, California; Baird Associates, Cambridge, Mass.

⁴⁵ Applied Research Laboratories, Glendale, California. Trade literature on the "Spectrograph Quantometer Adaptor."

graphic recording of spectral line intensities. The main advantage of the method is its speed, and it is generally claimed that a sample can be analysed for ten elements in under 3 minutes. The choice of spectrum line pairs is made easier since a much wider range of intensities can be measured than is practicable using photographic means; G. H. Dieke and H. M. Crosswhite,⁴⁶ for example, report that they have successfully used a pair of lines whose relative intensity ratio was 1 : 40,000. On the other hand, the comparatively large size of the photomultipliers, or of the mirrors used to direct the images of the spectrum lines on to them, makes it difficult to use lines which are close together.

It is apparent that this type of instrument is most valuable in those applications where large numbers of similar samples have to be analysed, and it is therefore eminently suitable for use in the control laboratories of large metallurgical works. When a complete survey of a material is required or when its impurities or constituents are not known the photographic method is of greater value, although direct-reading instruments in which the whole of the spectrum can be scanned by a single photocell can be used for this purpose.

The main disadvantage of direct-reading instruments is their high cost; a high-dispersion spectrograph is essential for a full application of the method, and the commercial instruments incorporate a specially designed grating spectrograph of the required characteristics; the recording apparatus is far from simple and for the best results a high-power controlled source unit is used for excitation.

It is generally claimed that the analytical accuracy of such an equipment is at least as high as the orthodox photographic method, and that, since the intensities of the spectrum lines used may vary between wide limits, a greater range of minor constituent concentrations may be satisfactorily covered.

Range of Application.—Although the most marked advances in emission spectrography in the past ten years have occurred in the analysis of metals, particularly light alloys, progress in other fields has been considerable. Many reviews of the scope of spectrographic methods have appeared in the literature, and its general application to specific branches of science has also been dealt with. For example, B. L. Clarke and A. E. Ruehle⁴⁷ have reviewed its applications in communications research, V. R. Ells⁴⁸ gives details of the spectrographic analysis of plant derivatives, and its use in agricultural investigations is reviewed by L. H. Rogers.⁴⁹ For these miscellaneous analyses it is customary to use an arc between carbon or graphite electrodes, the sample being held in a hole drilled in one or both of the electrodes. The analyses of water,⁵⁰ soil,⁵¹ fertilisers,⁵² and plants⁵³

⁴⁶ *J. Opt. Soc. Amer.*, 1946, **36**, 192.

⁴⁷ *Bell System Tech. J.*, 1938, **17**, 381.

⁴⁸ *J. Opt. Soc. Amer.*, 1941, **31**, 534.

⁴⁹ *Ibid.*, p. 260.

⁵⁰ L. W. Strock and S. Dexter, *ibid.*, p. 167.

⁵¹ R. O. Scott and R. L. Mitchell, *J. Soc. Chem. Ind.*, 1943, **62**, 4; G. W. Fox and R. A. Goodwin, *Iowa State Coll. J. Sci.*, 1941, **15**, 119; R. Q. Parks, *J. Opt. Soc. Amer.*, 1942, **32**, 233.

are of direct application in agricultural work, whilst in the biological field we find methods ranging from those dealing with food⁵⁴ to those which deal with traces of metallic and non-metallic derivatives in blood.⁵⁵ Arc excitation has also found wide application in the analysis of minerals, ores, and slags,⁵⁶ and a specific application to cement analysis is described by A. W. Helz.⁵⁷

Many of these materials, particularly those which are easily taken into solution, may be analysed by a flame technique.⁵⁸ An oxy-acetylene flame has been used for the analysis of fruit and plants,⁵⁹ and the Lundegårdh apparatus⁶⁰ has been adapted for the analysis of biological material in general.⁶¹ H. Lundegårdh and H. Bergstrand⁶² has used it for the examination of liver, the material being ashed and dissolved in acid before being atomised in the flame. Interesting modifications of the flame method produced by H. Ramage,⁶³ in which a spill of filter paper is impregnated with the solution under test, have been described by M. N. Thruston⁶⁴ and by F. C. Steward and J. A. Harrison.⁶⁵ The former method uses a copper arc in which to burn the filter paper, whilst the latter involves feeding the spill into the flame at a controlled rate to ensure regular spectral emission. Further developments in this field are described in Section 3 of this Report (p. 326).

For insulating materials a spark technique is usually employed. J. R. Churchill and R. G. Russell⁵⁶ pellet the material with sodium fluoride and graphite powder before sparking, and J. van Calker⁶⁶ has used a solid sample painted with a conducting material to enable the discharge to strike.

The halogens and certain non-metals may be detected by using a glow discharge in the vapour of the material, or by the use of spark excitation at reduced pressure. Using the spark technique, K. Pfeilsticker⁶⁷ has been able to detect the presence of gases in metallic electrodes.

⁵² E. H. Melvin and R. T. O'Connor, *Ind. Eng. Chem. Anal.*, 1941, **13**, 520; R. T. O'Connor, *ibid.*, p. 597.

⁵³ W. R. Brode and I. W. Wander, *J. Opt. Soc. Amer.*, 1941, **31**, 402; B. C. Brunstetter and A. J. Myers, *ibid.*, p. 163; M. L. Nichols and L. H. Rogers, *Ind. Eng. Chem. Anal.*, 1944, **16**, 137.

⁵⁴ J. K. Brody and D. T. Ewing, *ibid.*, 1945, **17**, 627; D. A. Harper and N. Strafford, *J. Soc. Chem. Ind.*, 1942, **61**, 74.

⁵⁵ A. Tracey and J. McPheat, *Biochem. J.*, 1943, **37**, 683.

⁵⁶ J. M. Bray, *Amer. Min.*, 1942, **27**, 769; W. W. A. Johnson and D. P. Norman, *Astrophys. J.*, 1943, **97**, 46; J. R. Churchill and R. G. Russell, *Ind. Eng. Chem. Anal.*, 1945, **17**, 66; C. G. Carlsson, *Jernkont. Ann.*, 1943, **127**, 572; P. D. Korzh, *Izvest. Akad. Nauk S.S.S.R.*, 1945, (Fiz), **9**, 665.

⁵⁷ *J. Res. Nat. Bur. Stand.*, 1945, **34**, 129.

⁵⁸ *Ann. Reports*, 1941, **38**, 274.

⁵⁹ M. A. Griggs, R. Johnston, and B. E. Elledge, *Ind. Eng. Chem. Anal.*, 1941, **13**, 99.

⁶⁰ H. Lundegårdh, "Die quantitative Spectralanalyse der Elemente," Jena, Gustav Fischer, Vol. 1, 1929; Vol. 2, 1934.

⁶¹ J. Cholak and D. M. Hubbard, *Ind. Eng. Chem. Anal.*, 1944, **16**, 728.

⁶² *Regiae Soc. Sci. Upsaliensis*, 1940, **12**, 1.

⁶³ *Nature*, 1936, **137**, 67.

⁶⁴ *Ann. Bot.*, 1939, **3**, 427.

⁶⁵ *Ibid.*, p. 424.

⁶⁶ *J. Soc. Chem. Ind.*, 1942, **61**, 144.

⁶⁷ *Spectrochim. Acta*, 1940, **1**, 403.

In the metallurgical field methods have been described for the investigation of inclusions and segregates in steel samples,⁶⁸ and a particularly interesting paper on this subject has been written by J. Convey and J. H. Oldfield.⁶⁹ In their apparatus the photographic plate moves in synchronism with a traversing spark, and so the image on the plate shows the point to point variation of the composition of the sample. The requirements for the application of spectrography to rapid foundry control were discussed in 1945 by H. W. Dietert and J. A. Schuch,⁷⁰ and, apart from the omission of recent developments in direct-reading equipment, the considerations put forward by these authors still apply. The application of normal spectrographic equipment to foundry control in England has recently been described by H. R. Clayton,⁷¹ the analysis having been accelerated by shortening the time spent in photographic processing. In this method an alloy may be analysed for 5 elements in less than 10 minutes.

H. R. C.

8. FLAME PHOTOMETRY.

The Lundegårdh method of exciting the emission spectrum of an element by atomisation of its solution and spraying into an air-acetylene flame has become firmly established as a standard spectrographic technique (see p. 325). Flame photometry represents a logical development of this procedure whereby the same means of spectrum excitation are employed, but the subsequent measurement of emission intensity is greatly simplified by the introduction of relatively cheap filters and direct-reading photocell-galvanometer combinations in place of the expensive spectrograph and associated equipment required for the photographic recording and determination of line intensities. In the typical flame photometer ordinary light filters are introduced to select those regions of the spectrum which contain suitable spectral lines of the particular element concerned and to cut out any radiation emitted by other elements present in the solution at the same time. This selection, of course, may be achieved far more precisely by means of monochromators¹ as in the case of the Beckman spectrophotometer attachment,² but the introduction of such devices detracts considerably from the simplicity and cheapness of the apparatus. The low emission energies available in such methods of direct photometry necessitate the adoption of extra sensitive means of detection (see p. 324). In simple flame photometry the use of relatively wide-band filters and the

⁶⁸ F. G. Barker, J. Convey, and J. H. Oldfield, *J. Iron Steel Inst.*, 1941, **144**, 143 F; R. Weihrich and W. Schwarz, *Arch. Eisenhüttenw.*, 1941, **15**, 83; G. Thanheiser and J. Heyes, *ibid.*, 1940, **14**, 543.

⁶⁹ *J. Iron Steel Inst.*, 1945, **152**, 473 F.

⁷⁰ *Trans. Amer. Found. Assoc.*, 1945, **52**, 889.

⁷¹ *J. Soc. Chem. Ind.*, 1948, **67**, 270.

¹ G. Thanheiser and J. Heyes, *Mitt. Kaiser Wilhelm Inst. Eisenforsch.*, 1937, **19**, 113; 1939, **21**, 327; W. H. Jansen, J. Heyes, and C. Richter, *Z. physikal. Chem.*, 1935, **A**, **174**, 291; J. Heyes, *Angew. Chem.*, 1937, **50**, 871.

² R. H. Müller, *Anal. Chem.*, 1947, **19**, No. 8, 21A.

consequent increase in available radiant energy enables the experimenter to employ less elaborate detectors such as barrier layer cells or photo-electric cells in conjunction with a sensitive galvanometer. Visual methods employing filters have also been described³ but are usually not to be recommended for routine work.⁴ The photometer is calibrated against solutions containing known amounts of the element under test, the range of concentration being determined by the sensitivity of the detector galvanometer combination. For low concentrations, *e.g.*, up to 10 p.p.m. of sodium, a linear relationship has been found between concentration and galvanometer reading, but for higher concentrations a calibration curve is usually required.⁵

The key factor in flame photometry is, of course, the efficiency of the filters in cutting out unwanted radiation. Sodium light is particularly difficult to eliminate and early attempts to determine potassium in the presence of sodium by substituting filters for monochromators were only partly successful.⁶ Combinations of filters such as Jena (Schott) types RG9 and BG17 proved to be more efficient than single filters. W. Schuhknecht⁷ obtained a satisfactory separation using a combination of three filters, BG19, RG8, and BG3, and by means of a gas-filled photocell and sensitive galvanometer, was able to determine potassium in solution as chloride with an accuracy of $\pm 5\%$ over the range 0.04—0.008% of K_2O . He claimed that interference due to sodium, calcium, and magnesium, also present in the solution, was negligible.

In 1938 a flame photometer based on this design was produced by the firm of Zeiss for the routine determination of potassium. It employed a gravity feed for the test solution to the atomiser, and a special filter: the filtered radiation was measured with a caesium photocell and mirror galvanometer. At the same time Messrs. Siemens introduced a model with a suction feed, an all-glass atomiser, and a single filter (RG8): by means of a stabilised amplifier, the photocell currents could be read on an ordinary milliammeter. Both these instruments underwent exhaustive tests in the analysis of plant, food, and fertiliser extracts,^{4, 8} and in general the results agreed well with the figures for potassium as determined by chemical analysis, down to a concentration of 20 mg. of K_2O per 100 c.c. The outstanding feature of this new technique was the ease and rapidity with which the analyses could be made, the average time for each determination being about 2 minutes. The majority of the investigators found the photocell-galvanometer combination to be more reliable as a means of detection because of instability in the photocell amplifier. Using a similar technique and the combination of filters RG19, RG8, and BG3, H. Lundegårdh and

³ S. Goy, *Angew. Chem.*, 1937, **50**, 301.

⁴ L. Schmitt and W. Breitweiser, *Bodenk. Pflanz.*, 1938, **10**, 750.

⁵ *Ind. Eng. Chem. Anal.*, 1945, **17**, 605.

⁶ Jansen, Heyes, and Richter, *loc. cit.*, ref. 1. ⁷ *Angew. Chem.*, 1937, **50**, 299.

⁸ F. Kertscher, *Bodenk. Pflanz.*, 1938, **10**, 758; W. Lehmann, *ibid.*, p. 766; F. Geissecke and W. Rathje, *ibid.*, p. 776; L. Rohmlehrer, *Mezogs. Kutat.*, 1944, **17**, 51; *Chem. Abs.*, 1947, **41**, 7165.

K. Boratynski⁹ concluded that the method might be used successfully for the routine determination of potassium over the range 0.00025—0.004M. with an accuracy of $\pm 10\%$.

Further work revealed that interference due to the presence of other elements, particularly calcium in soil extracts, could seriously affect the accuracy of the potassium determinations. Substitution of the filter RG8 by RG9 improved the performance of the instrument, but it was still unsatisfactory and various other suggestions were made to overcome this interference such as precipitation of the calcium and the use of illuminating gas instead of acetylene, whereby the intensity of the calcium radiation was reduced owing to the lower flame temperature produced.¹⁰ The addition of ammonium phosphate and calibration of the instrument with potassium in ammonium nitrate solution was also recommended.¹¹

Various modifications were proposed, particularly in the design of the atomiser and burner, to increase the accuracy and adaptability of the apparatus and to allow for the substitution of ordinary illuminating gas.¹² S. D. Boon¹³ discusses in some detail the development of the flame photometric technique and gives much valuable information as to the relative merits of different types of filters and photocells together with a description of the apparatus used in his investigations. A somewhat similar design has been described for the determination of sodium and potassium in biological fluids¹⁴ and for the determination of serum potassium using an Ilford filter 609 and Cintel GS18 photocell.¹⁵ Results obtained with this photometer agreed with chemical determinations of potassium within 2 mg. per 100 c.c. Filters based on compounds of the rare earths praseodymium, neodymium, and dysprosium (*e.g.*, Wratten No. 77, Chance ON16) have strong absorption bands in the region of the intense sodium lines (5890, 5896 Å.) and have been used successfully for the elimination of this element.

R. B. Barnes, D. Richardson, J. W. Berry, and R. L. Hood⁵ describe a much more compact apparatus designed for routine laboratory use, incorporating a metal atomiser with gravity feed, an ordinary Meker-type Fisher burner, and a barrier-layer cell with galvanometer. Domestic coal gas is used, and the monitoring of the gas and air supplies is achieved by pressure gauges instead of the more cumbersome manometers of earlier designs. Various Corning glass filters are described for the determination of sodium, potassium, calcium, and lithium. A number of experimental models based

⁹ *Svensk Kem. Tidskr.*, 1938, **50**, 135.

¹⁰ H. Riehm, *Bodenk. Pflanz.*, 1945, **36**, 109.

¹¹ K. Nehring, *Chim. et Ind.*, 1942, **30**, 36; G. Varrallyay, *Mezogs. Kutat.*, 1944, **17**, 95; *Chim. et Ind.*, 1946, **56**, 413.

¹² H. Riehm, *Bodenk. Pflanz.*, 1940, **21/22**, 277; E. Rauteberg and E. Knippenberg, *ibid.*, 1940, **20**, 364; *Ernähr. Pflanz.*, 1941, **37**, 73; H. Riehm, *Bodenk. Pflanz.*, 1942, **28**, 246; R. Hermann and P. Lederle, *ibid.*, 1942, **30**, 189; R. Hermann, *Forsch. Dienst*, 1943, **16**, 239.

¹³ "Vlam-fotometrie," D. B. Centen's, Amsterdam, 1945.

¹⁴ W. R. Domingo, W. Klyne, and W. Weedon, *Biochem. J.*, 1948, **42**, xxxvi.

¹⁵ W. Klyne, *ibid.*, 1948, **43**, xxv.

on this design were produced by the American Cyanamid Co., but a similar model made by the Perkin Elmer Corporation is commercially available. Using these instruments, the applicability of the flame photometric technique has been thoroughly investigated.¹⁶ The design of the atomiser would appear to be most critical, and in particular cases¹⁷ metal types with suction feed were found preferable to all glass types. Further improvements in design have also been suggested.¹⁸ Satisfactory results, it is claimed,¹⁷ could only be obtained when a more uniform gas supply (cylinder gas) was substituted for the mains supply.

The technique involves a number of possible sources of error: (a) Variations in the gas and air supplies which affect the temperature of the flame and therefore the intensity of emission; (b) non-uniformity of the spray which is dependent upon the air pressure and atomiser; (c) surface-tension and viscosity differences between standard and test solutions affecting the rate of atomisation; (d) mutual interference between elements in the flame; and (e) filter limitations. Most of these factors have been discussed in relation to the flame excitation technique as used in spectrographic work and are admirably reviewed by R. L. Mitchell¹⁹ and others.²⁰ For pure solutions, results consistent within $\pm 3\%$ have been obtained without undue difficulty,⁵ but for complex solutions, like biological extracts, extra precautions are necessary. The presence of acids, bases, or salts affects the accuracy of the analyses to a varying degree according to their concentration in the solutions. Most biological extracts, for example, are obtained by acid digestion, but because of their interference in the extracts, acids cannot be used indiscriminately. Certain acids are particularly troublesome; the presence of 0.01% of phosphoric acid is sufficient to cause a decrease of 14% in the estimation of sodium and 9% in that of potassium compared with the readings obtained for these two metals in pure solutions.²¹ Even in pure solutions, the nature of the anion affects the calibration of the instrument⁵ and must therefore be taken into consideration. Errors due to the presence of other cations are generally small unless they occur at a concentration equivalent to or greater than that of the test element, in which case they may interfere quite seriously and must be allowed for. Alcohol and acetic acid give rise to positive errors in the determination of potassium and sodium in all cases where they occur at concentrations greater than 1%.²¹ It is therefore evident that great

¹⁶ O. J. Attoe and R. Truog, *Soil Sci. Soc. Amer. Proc.*, 1946, **11**, 221; R. R. Overman and A. K. Davis, *J. Biol. Chem.*, 1947, **168**, 641; P. M. Hald, *ibid.*, 1947, **167**, 499; T. D. Parkes, H. O. Johnson, and L. Lykken, *Anal. Chem.*, 1948, **20**, 827; S. J. Toth, A. L. Prince, A. Wallace, and D. S. Mikkelsen, *Soil Sci.*, 1948, **66**, 450.

¹⁷ Hald, *loc. cit.*, ref. 16.

¹⁸ A. T. Myers, *Ind. Eng. Chem. Anal.*, 1946, **18**, 585; V. Toscani, *ibid.*, 1947, **19**, 820.

¹⁹ "The Spectrographic Analysis of Soils, Plants and Related Materials," Tech. Comm. Bur. Soil Sci., 1948, No. 44.

²⁰ H. C. T. Stace, *J. Proc. Austral. Chem. Inst.*, 1947, **14**, 144.

²¹ Parkes, Johnson, and Lykken, *loc. cit.*, ref. 16.

care has to be taken before the simple flame photometer may be used for a particular investigation.

The usual procedure adopted has been to calibrate the photometer with solutions approximating in composition to that under test, and in this way fairly reliable results can be obtained. This method, however, is not always practicable, and for this reason an internal-standard technique has been suggested²² whereby any change affecting the light intensity due to one element affects the internal standard in the same way. Using a specially modified photometer to enable them to measure independently the radiation due to both test element and internal standard, the authors have appreciably increased the accuracy of the technique. By adopting the standard method of analysis with this modified instrument it becomes quite feasible to determine two elements in the same solution at the same time.

The flame photometric technique has been successfully used for the determination of boron as methyl borate with a sensitivity down to 5 μ g. of the element per ml.¹³ Other rapid methods for the determination of this element based on similar principles have also been described.²³

Hence, although flame photometry is obviously a rather crude technique and certainly limited in its applications, it nevertheless possesses certain advantages over spectrographic methods, particularly when factors like cost and simplicity in operation have to be considered. Constructional and maintenance costs are negligible compared with those of the more elaborate spectrograph, and with a certain amount of care and preparation, consistent results can be obtained even by relatively unskilled operators. The method has already proved to be particularly valuable for the routine determination of sodium, potassium, and calcium in biological fluids and extracts, but might well be adapted for the analysis of other elements which are excited at flame temperatures provided that satisfactory filters can be found.

L. L.

4. VOLUMETRIC ANALYSIS.

Solutions and Standards for Volumetric Analysis.—Since the last Report¹ much work has been carried out in this important but unrewarding field, and many valuable collaborative studies have been sponsored by the Association of Official Agricultural Chemists. Dipotassium paraperiodate, $K_2H_3IO_6 \cdot 3H_2O$,² salicylic acid,³ and *o*-chlorobenzoic acid⁴ have been proposed as acidimetric standards, but although sulphamic acid, NH_2SO_3H ,

²² J. W. Berry, D. G. Chappell, and R. B. Barnes, *Ind. Eng. Chem. Anal.*, 1946, 18, 19.

²³ J. S. McHargue and R. K. Calfee, *ibid.*, 1932, 4, 385; 1937, 9, 288; H. C. Weber and R. D. Jacobson, *ibid.*, 1938, 10, 273.

¹ *Ann. Reports*, 1937, 34, 480.

² L. Malaprade, *Cong. Chim. ind., Compt. rend. 18me Cong., Nancy*, 1938, 91; *Chem. Abs.*, 1939, 33, 6192.

³ E. Latiu, *Z. anal. Chem.*, 1943, 126, 184.

⁴ I. G. Murgulescu and V. Alexa, *ibid.*, 1943, 125, 260.

has the advantage of being a strong acid and relatively soluble in water,⁵ hydrochloric acid prepared by the constant boiling-point method still appears to be more exact and convenient to prepare.⁶

It is now generally agreed that a temperature of 300° should not be exceeded when heating sodium hydrogen carbonate for the preparation of anhydrous sodium carbonate,⁷ but W. R. Carmody⁸ states that up to 0.1% of water is held tenaciously but can be partly eliminated by powdering and re-igniting. The standardisation of acids against sodium carbonate and borax has been studied collaboratively,⁹ and W. Young¹⁰ proposes *s*-diphenylguanidine as a primary standard, and A. J. Berry¹¹ advocates thallos carbonate, which has a high equivalent weight and serves as a link with iodometric standards since it is quantitatively oxidised by iodate in acid solution to the thallic state. Silver hydroxide prepared from pure silver has been used to standardise acids, halides, thiocyanate, and silver nitrate.¹²

The stabilisation of solutions of sodium thiosulphate continues to attract attention,¹³ though it appears that sterile solutions of pH not greater than 6.2 maintain their titre for long periods.¹⁴ C. W. Jordan¹⁵ deprecates the use of borax as a preservative, but to safeguard against adventitious inoculation by sulphur bacteria, sodium benzoate,¹⁶ chloroform,¹⁷ mercuric iodide,¹⁸ and amyl¹⁹ and octyl²⁰ alcohol have been suggested. Chloroform and mercuric iodide effectively stabilised solutions stored at 40° for two months, but alkalis promoted decomposition.¹⁸ Although pure crystalline sodium thiosulphate pentahydrate slowly decomposes in the solid state,²¹ the anhydrous salt is thermally stable for 79 days at 120° and has been proposed as a primary standard.²² Changes in the composition of standard

⁵ S. M. J. Butler, G. F. Smith, and L. F. Audrieth, *Ind. Eng. Chem. Anal.*, 1938, **10**, 690.

⁶ W. H. King, *J. Assoc. Off. Agric. Chem.*, 1942, **25**, 653.

⁷ L. Ramberg, *Svensk Kem. Tidskr.*, 1940, **52**, 137.

⁸ *Ind. Eng. Chem. Anal.*, 1945, **17**, 577.

⁹ L. Vandaveer, *J. Assoc. Off. Agric. Chem.*, 1939, **22**, 563; H. W. Conroy, *ibid.*, 1941, **24**, 636.

¹⁰ *Canadian J. Res.*, 1939, **17**, B, 192.

¹¹ *Analyst*, 1939, **64**, 27; cf. E. Jensen and B. Nilssen, *Ind. Eng. Chem. Anal.*, 1939, **11**, 508.

¹² L. G. Escobar, *Anal. Fis. Quím.*, 1945, **41**, 1071, 1086; 1946, **42**, 203, 211.

¹³ *Ann. Reports*, 1935, **32**, 454.

¹⁴ J. L. Kassner and E. E. Kassner, *Ind. Eng. Chem. Anal.*, 1940, **12**, 655; G. M. Johnson, *J. Assoc. Off. Agric. Chem.*, 1942, **25**, 659; 1945, **28**, 594.

¹⁵ *Amer. J. Pharm.*, 1938, **110**, 316.

¹⁶ J. Ehrlich, *Ind. Eng. Chem. Anal.*, 1942, **14**, 406.

¹⁷ Kassner and Kassner, *loc. cit.*, ref. 14; S. O. Rue, *Ind. Eng. Chem. Anal.*, 1942, **14**, 802.

¹⁸ *Idem*, *ibid.*

¹⁹ Johnson, *loc. cit.*, ref. 14; A. Baudouin and (Mlle.) P. Hillion, *Bull. Soc. Chim. biol.*, 1944, **26**, 490.

²⁰ *Idem*, *ibid.*

²¹ V. K. LaMer and H. M. Tomlinson, *Ind. Eng. Chem. Anal.*, 1937, **9**, 588.

²² H. M. Tomlinson and F. G. Ciapetta, *ibid.*, 1941, **13**, 539.

iodine solutions have been discussed by C. K. Banks,²³ and for standardisation of thiosulphate it is invariably obtained from potassium iodide by oxidation with potassium dichromate²⁴ (a reaction effectively catalysed by cupric ions²⁵), or by potassium iodate or better cupric perchlorate;²⁶ addition of potassium thiocyanate improves the end-point.²⁷

Pure potassium iodide has been prepared²⁸ and examined as a primary standard in permanganatometry²⁹ and arsenious oxide can be used in preference to oxalate¹ if a suitable catalyst (*e.g.*, iodine chloride) is present.³⁰ Other oxidants such as potassium dichromate,³¹ iodate,³² bromide-bromate,³³ and cerate solutions³⁴ have been carefully studied, and E. C. Deal³⁵ reports on the standardisation and stability of thiocyanate solutions. Solutions of sodium hypochlorite retain their titre in the dark³⁶ and when strongly basified³⁷ and are preferred to bromate in the determination of antimony and other substances.^{36, 38} For some purposes they can be replaced by solutions of chloramine-T.³⁹ More work has been carried out on the reactions of sodium chlorite,⁴⁰ and its potentialities as a volumetric reagent.⁴¹ Where acidified bromate-bromide mixtures are inappropriate a solution of bromine in potassium bromide can be stored and dispensed from apparatus described by A. J. Henry.⁴²

With regard to reducing agents, stable solutions of mercurous perchlorate have been used for the determination of ferric iron though the reaction is not strictly stoichiometric.⁴³ Agreement has not yet been reached on the best means of standardising titanous chloride⁴⁴ but the use of buffers to increase the pH and raise its reduction potential is well

²³ *J. Amer. Pharm. Assoc.*, 1948, **37**, 6.

²⁴ Johnson, *loc. cit.*, ref. 14.

²⁵ B. D. Sully, *J.*, 1942, 366.

²⁶ J. J. Kolb, *Ind. Eng. Chem. Anal.*, 1944, **16**, 38.

²⁷ G. C. Oglethorpe and C. G. Smith, *Analyst*, 1943, **68**, 325.

²⁸ J. J. Lingane and I. M. Kolthoff, "Inorganic Syntheses," New York, 1939, p. 163.

²⁹ I. M. Kolthoff, H. A. Laitinen, and J. J. Lingane, *J. Amer. Chem. Soc.*, 1937, **59**, 429; 1939, **61**, 1690.

³⁰ D. E. Metzler, R. J. Myers, and E. H. Swift, *Ind. Eng. Chem. Anal.*, 1944, **16**, 625.

³¹ J. R. Pound, *Chem. Eng. Min. Rev.*, 1945, **38**, 87.

³² S. M. Berman, *J. Assoc. Off. Agric. Chem.*, 1937, **20**, 590.

³³ H. C. Van Dams, *ibid.*, 1947, **30**, 502.

³⁴ G. F. Smith and C. A. Getz, *Ind. Eng. Chem. Anal.*, 1940, **12**, 339.

³⁵ *J. Assoc. Off. Agric. Chem.*, 1942, **25**, 661; 1945, **28**, 595; 1947, **30**, 496.

³⁶ J. Bitskei, *Magyar Chem. Fol.*, 1944, **50**, 97.

³⁷ N. I. Goldstone and M. B. Jacobs, *Ind. Eng. Chem. Anal.*, 1944, **16**, 206.

³⁸ J. Bitskei and K. Petrich, *Magyar Chem. Lapja*, 1947, **2**, 230.

³⁹ D'Costas G. Macris, *Ann. Chim. analyt.*, 1946, **28**, 165; B. Samek, *Časopis českoslov. Lék.*, 1941, **21**, 77.

⁴⁰ M. C. Taylor, J. F. White, G. P. Vincent, and G. L. Cunningham, *Ind. Eng. Chem.*, 1940, **32**, 899.

⁴¹ D. T. Jackson and J. L. Parsons, *Ind. Eng. Chem. Anal.*, 1937, **9**, 14; L. F. Yntema and T. Fleming, *ibid.*, 1939, **11**, 375.

⁴² *Analyst*, 1945, **70**, 259.

⁴³ W. Pugh, *J.*, 1945, 588.

⁴⁴ J. E. Breit, *J. Assoc. Off. Agric. Chem.*, 1947, **30**, 504.

established.⁴⁵ J. E. Lindsay⁴⁶ has examined electrolytic iron as a standard, and ferrous ethylenediamine sulphate, $[\text{C}_2\text{H}_4(\text{NH}_2)_2]_2\text{SO}_4 \cdot \text{FeSO}_4 \cdot 4\text{H}_2\text{O}$, is found to be much more stable than Mohr's salt.⁴⁷ F. R. Duke⁴⁸ ensures complete reduction of standard ferrous solutions by running them down a column of lead amalgam just before use. The simple and direct preparation of chromous chloride or sulphate solutions of determinate concentration described by J. J. Lingane and R. L. Pecsok⁴⁹ should facilitate the extended use of this powerful reducing agent whose storage, standardisation, and reactions have recently been reviewed.^{49, 50}

Rapid methods have been described for preparing standard solutions of almost all the reagents in common use in volumetric analysis.⁵¹ When these are dispensed from a large storage reservoir and replaced by dry air the evaporation of water to restore saturation conditions must cause an increase in the concentration of the residual solution, but H. A. Liebhavsky⁵² has shown that the error is quite negligible.

In view of the great importance of accurate pH measurements to the analyst it will not be inappropriate to recall that the pH of 0.05M-borax is now stated⁵³ to be 9.18 at 20°. Acid salts of benzoic, phenylacetic, and other organic acids give highly buffered solutions suitable as pH standards,⁵⁴ and saturated potassium hydrogen tartrate solution is said to be better than aqueous potassium hydrogen phthalate.⁵⁵

Apparatus.—Drastic modification in the design of apparatus for macrovolumetric analysis is scarcely to be expected, though minor improvements continue to be made. For instance, J. T. Stock and M. A. Fill⁵⁶ propose two methods of modifying burette taps to effect finer control of delivery, and F. C. Guthrie⁵⁷ describes a simple reading device. Copiously illustrated and referenced reviews of microvolumetric apparatus have been given by G. H. Wyatt,⁵⁸ and by R. Belcher and C. L. Wilson.⁵⁹ On this scale tapless burettes are increasingly used.⁶⁰ An entirely new type of microburette designed by J. A. Saunders,⁶¹ an electrically operated burette,⁶² and devices

⁴⁵ O. L. Evenson, *J. Assoc. Off. Agric. Chem.*, 1945, **28**, 633; P. G. Butts, W. J. Meikle, J. Shovers, D. L. Kouba, and W. W. Becker, *Anal. Chem.*, 1948, **20**, 947.

⁴⁶ *Chemist Analyst*, 1942, **31**, 8.

⁴⁷ K. P. Caraway and R. E. Oesper, *J. Chem. Educ.*, 1947, **24**, 235.

⁴⁸ *Ind. Eng. Chem. Anal.*, 1945, **17**, 530.

⁴⁹ *Anal. Chem.*, 1948, **20**, 425.

⁵⁰ H. W. Stone, *ibid.*, p. 747; R. Flatt and F. Sommer, *Helv. Chim. Acta*, 1942, **25**, 684.

⁵¹ E. Shulek and F. Szeghő, *Z. anal. Chem.*, 1942, **123**, 252.

⁵² *Ind. Eng. Chem. Anal.*, 1944, **16**, 349.

⁵³ A. D. E. Lauchlan, *Nature*, 1944, **154**, 577.

⁵⁴ J. C. Speakman and N. Smith, *ibid.*, 1944, **155**, 698.

⁵⁵ J. J. Lingane, *Anal. Chem.*, 1947, **19**, 810.

⁵⁶ *Analyst*, 1946, **71**, 142.

⁵⁷ *Chem. and Ind.*, 1947, 240.

⁵⁸ *Analyst*, 1944, **69**, 81, 180.

⁵⁹ *Metallurgia*, 1946, **34**, 337; **35**, 47.

⁶⁰ I. Lüttgert and E. Schröer, *Z. physikal. Chem.*, 1941, **49**, B, 257.

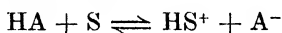
⁶¹ *Analyst*, 1946, **71**, 528.

⁶² F. C. Nachod, *Ind. Eng. Chem. Anal.*, 1945, **17**, 602.

for varying the rate of efflux⁶³ and for obtaining drops as small as 0.1 mm. in diameter⁶⁴ may also be noted. By fabricating a glass electrode in the form of a re-entrant bulb of capacity ~1.5 ml. W. Ingold⁶⁵ is able to titrate 300—900 $\mu\text{g.}$ of acid with an accuracy of $\pm 5\%$. The principle of the hypodermic syringe from which the displacement of liquid is controlled by a micrometer screw underlies many precision micro-pipettes and burettes described recently.⁶⁶ When such apparatus is motor-driven, the rate and extent of the delivery of titrating fluid can be controlled by potential changes of indicator electrodes in solution so that potentiometric titrations can be carried out and recorded automatically.⁶⁷ An alternative system in which the titrant is added at a constant rate has been described by Gonzalez Barredo and Taylor.⁶⁶ Benedetti-Pichler has considered the possible errors arising from the evaporation of standard solutions from the tips of micro-burettes⁶⁸ and describes the technique of titration with $\mu\text{g.}$ samples where a low-power microscope is needed to observe operations conducted with the aid of mechanical manipulators.⁶⁹

Titration in Non-aqueous Solvents.—Where the material to be titrated is insoluble in water, solvents such as ethyl, *n*-butyl, and amyl alcohol or acetone have often been substituted. A. E. Ruehle⁷⁰ extends the range to dioxan and ethylene glycol monoalkyl ethers (Cellosolves) with anisole recommended as a solvent for pitches and asphalts in titrations against potassium hydroxide and sodium butoxide. E. Turk and E. E. Reid⁷¹ use alcohol or naphtha as a solvent for thiols in titrations with copper alkyl phthalates.

That non-aqueous solvents may provide a solution to the problems involved in determining certain salts, or acids and bases too weak for titration by conventional methods in aqueous solution, follows from a consideration of Brønsted's equation



For if the solvent S used is more basic than the conjugate base A^- of the acid HA which is to be determined, equilibrium will be displaced appreciably to the right. Acids which are weak in water will thus appear stronger in a more basic solvent. Conversely, weak bases will appear stronger when water is replaced by a more acidic solvent, as was first demonstrated experi-

⁶³ J. T. Stock and M. A. Fill, *Metallurgia*, 1944, **31**, 103; F. P. W. Winteringham, *Analyst*, 1945, **70**, 173.

⁶⁴ W. R. Lane, *J. Sci. Instr.*, 1947, **24**, 98.

⁶⁵ *Helv. Chim. Acta*, 1946, **29**, 1929.

⁶⁶ P. A. Shaffer, P. S. Farrington, and C. Niemann, *Anal. Chem.*, 1947, **19**, 492; cf. G. H. Wyatt, *Metallurgia*, 1945, **32**, 240; V. Stott and (Miss) I. H. Hadfield, B.P. 584,841; J. J. Lingane, *Anal. Chem.*, 1948, **20**, 285; H. A. Robinson, *Trans. Electrochem. Soc.*, 1947, **92**, Preprint 38, 503; J. M. Gonzalez Barredo and J. K. Taylor, *ibid.*, Preprint 26, 303.

⁶⁷ Lingane; Robinson, *loc. cit.*

⁶⁸ A. A. Benedetti-Pichler and S. Siggia, *Ind. Eng. Chem. Anal.*, 1942, **14**, 662.

⁶⁹ A. G. Loscalzo and A. A. Benedetti-Pichler, *ibid.*, 1945, **17**, 187.

⁷⁰ *Ind. Eng. Chem. Anal.*, 1938, **10**, 130. ⁷¹ *Ibid.*, 1945, **17**, 713.

mentally by N. F. Hall and J. B. Conant.⁷² For reactions with glacial acetic acid as solvent the titrant is prepared by adding acetic anhydride to aqueous perchloric acid in proportion to its water content, diluting with acetic acid to the desired strength, and standardising against anhydrous sodium carbonate.⁷³ Blumrich and Bandel⁷³ found that primary, secondary, and tertiary amines (but not amides of carboxylic acids or acetylated amines) could be titrated potentiometrically: the titre after acetylation of a mixture thus gave the amount of tertiary amine alone.⁷³ Up to 50% of water in a sample is admissible but a special procedure must be adopted when sterically hindered secondary amines are present.⁷⁴ Since salicylaldehyde condenses with ammonia and primary (but not secondary or tertiary) amines to form azomethines of decreased basicity, a method becomes available for determining all the components of an ammonia-amine mixture.⁷⁵ When less than 0.2% of water is present, many organic bases and amino-acids and alkali, alkaline-earth, and ammonium salts of carboxylic acids behave as strong bases in glacial acetic acid and can be titrated with 0.2N-perchloric acid, crystal-violet, thymol-blue, and neutral-red being used as visual indicators.⁷⁶ α -Naphtholbenzein is preferred for dimethylaniline⁷⁷ and quinine, the latter titrating as a di-acid base.⁷⁸ In chloroform the cinchona bases and nicotine are accurately titratable as di-acid bases with toluene-*p*-sulphonic acid and picric acid, respectively, dimethyl-yellow being the indicator. However, in aqueous alcohol they both behave as mono-acid bases towards mineral acids (methyl-red) thus permitting an assay of nicotine in tobacco.⁷⁹ Salts of weak monobasic organic acids (notably the "soaps") dissolve quite readily in 1 : 2-glycols and better still in admixtures with higher aliphatic alcohols or chlorinated solvents and can be titrated directly with solutions of hydrochloric, perchloric, or other strong acids in the same solvent, the end-point being determined potentiometrically or visually.⁸⁰ Phenolphthalein and methyl-red can be used in a double-indicator method to determine free alkali and soap, and salts of inorganic acids such as metaborates, aluminates, etc., mixtures of weak and strong acids, and weak bases can be determined in the same solvent.⁸¹

Weak acids can be titrated if the solvent is more basic than water, but to minimise solvolysis it should have a small autoprotolysis constant and the titrant must naturally be even more basic than the solvent. Using anhydrous ethylenediamine as solvent and sodium 2-aminoethoxide as titrant,

⁷² *J. Amer. Chem. Soc.*, 1927, **49**, 3047, 3062; 1930, **52**, 5115.

⁷³ K. Blumrich and G. Bandel, *Angew. Chem.*, 1941, **54**, 374; H. Haslam and P. F. Hearn, *Analyst*, 1944, **69**, 144.

⁷⁴ C. D. Wagner, R. H. Brown, and E. D. Peters, *J. Amer. Chem. Soc.*, 1947, **69**, 2809.

⁷⁵ *Idem*, *ibid.*, p. 2611.

⁷⁶ J. C. Oppenheim, *J. Soc. Chem. Ind. Victoria*, 1945, **45**, 647.

⁷⁷ Haslam and Hearn, *loc. cit.*, ref. 4.

⁷⁸ R. L. Herd, *J. Amer. Pharm. Assoc.*, 1942, **31**, 9.

⁷⁹ E. M. Trautner and O. E. Neufeld, *Australian Chem. Inst.*, 1946, **13**, 70.

⁸⁰ S. R. Palit, *Ind. Eng. Chem. Anal.*, 1946, **18**, 246.

⁸¹ *Idem*, *Oil and Soap*, 1946, **23**, 58.

M. L. Moss, J. H. Elliot, and R. T. Hall⁸² find that aromatic carboxylic acids and phenols behave as strong acids and give very satisfactory inflections in potentiometric titration curves. Amino-acids titrate as simple carboxylic acids and salicylic acid behaves as a dibasic acid. Even resorcinol gives two inflections, the second being that of a very weak acid, and all three stages of dissociation of boric acid are detectable. In acetic anhydride as solvent, sodium acetate acts as a strong base, changing indicators such as methyl-orange to their alkaline colour and reacting instantaneously with trichloroacetic acid and more slowly with acid chlorides.⁸³

In addition to work in aqueous alcohol,⁸⁴ acetone,⁸⁵ and glacial acetic acid,^{72-78, 86} there are many scattered observations relating to titrations in non-aqueous solvents and there can be little doubt that this subject will steadily gain importance as its potentialities come to be more generally realised.

Coulometric Analysis.—The previous sections will have exemplified evolutionary trends in classical volumetric analysis, and the search for greater speed and accuracy with ever smaller samples of material. The inconvenience of having to prepare standard solutions, the difficulties inherent in their maintenance, and problems of burette design and instrumentation could be circumvented if the titrant could be generated *in situ* by an electrolytic method. This was first realised experimentally by L. Szebellédy and Z. Somogyi,⁸⁷ who standardised hydrochloric acid by adding potassium chloride and passing an approximately constant current between a platinum cathode and a silver anode until the change in colour of bromocresol-green showed that neutralisation was complete. The quantity of electricity employed was measured by a silver weight coulometer in series and the extent of chemical action was calculated from this, and the known value of the Faraday, 100% current efficiency being assumed. This procedure, described appropriately as coulometry, was extended to the standardisation of sulphuric acid, and coulometric determinations of thiocyanate, hydrazine, hydroxylamine, and even caustic alkali could be effected by generating bromine electrolytically.

Though capable of very precise results, applications were limited (since the electrode potentials were not controlled) to cases where a single cell reaction could take place and where a specific indicator was available, whilst the use of a weight coulometer was an obvious disadvantage. Now all oxidation-reduction processes involve electron transfer; and whether this is effected electrolytically at suitable electrodes or by means of an appropriate oxidising or reducing standard solution is dictated sometimes by choice, sometimes by necessity. Though Szebellédy and Somogyi applied

⁸² *Anal. Chem.*, 1948, **20**, 784.

⁸³ M. Usanovitch and K. Jazimirski, *J. Gen. Chem. Russia*, 1941, **11**, 957.

⁸⁴ H. Baggesgaard-Rasmussen, *Z. anal. Chem.*, 1936, **105**, 269.

⁸⁵ G. M. Richardson, *Proc. Roy. Soc.*, 1934, **B**, **115**, 121, 142, 170, 180.

⁸⁶ I. M. Kolthoff and A. Willan, *J. Amer. Chem. Soc.*, 1934, **56**, 1014; G. F. Nadeau and L. E. Branchen, *ibid.*, 1935, **57**, 1363.

⁸⁷ *Z. anal. Chem.*, 1938, **112**, 313, 323, 332, 385, 391, 395, 400.

their coulometric technique only to familiar volumetric determinations, no such arbitrary limitation is necessary, for all electrochemical determinations can legitimately be included within its scope. Provided the electrode reaction is reproducible and exactly defined in a stoichiometric sense, it need be neither chemically nor thermodynamically reversible. With mixtures of reducible ions, control of potential becomes imperative, and J. J. Lingane⁸⁸ points out that a mercury-pool cathode with a silver-silver chloride anode possesses many advantages since it is relatively easy to obtain 100% current efficiency in the electrolytic reduction of certain organic compounds⁸⁹ and various metal ions,⁹⁰ whilst conventional polarographic methods serve to establish optimum conditions of cathode potential and electrolyte composition and concentration for any specific determination. Lingane developed a hydrogen-oxygen coulometer as a direct-reading instrument to indicate continuously the progress of an electrolysis,⁸⁸ and the potential control can be effected manually or automatically.⁹¹

During electrolysis at constant potential the current decreases exponentially with time, and each determination would theoretically require an infinite time for its completion. In practice 99% reduction is achieved (irrespective of the initial concentration) by the time the current has dropped to 1% of its original value and little is gained by pursuing the electrolysis further. If a constant electrolysing current is employed some means of detecting the end-point must be provided. J. Epstein, H. A. Sober, and S. D. Silver⁹² determine acid gases in the air (or materials which can be pyrolysed to acids) by absorbing them in the cathode chamber of a U-shaped electrolysis vessel and titrating with hydroxyl ions generated by the electrolysis of sodium bromide. The end-point is determined potentiometrically by a Pinkhof system, and since a constant current is employed the time taken for complete neutralisation is a measure of the acid present.

Unstable bromine solutions are an inconvenient feature in the determination of di-(2-chloroethyl) sulphide by oxidation of thiodiglycol prepared therefrom by hydrolysis) to its sulphoxide, and J. W. Sease, C. Niemann, and E. H. Swift eliminate them by generating the bromine electrolytically in an apparatus suitable for the determination of $\mu\text{g.}$ quantities of thiodiglycol⁹³ or 30—1000 $\mu\text{g.}$ of arsenic.⁹⁴ The constant current of less than 10 ma. is derived from a dry storage battery, and the coulometer is replaced by a stop-watch. Polarised electrodes are used to detect the end-point in what is effectively a combination of the dead-stop end-point⁹⁵ and an amperometric titration, for since the concentration of bromine in excess determines the rate of diffusion of this element to the indicator cathode and thus the amount of depolarisation, the magnitude of the indicator current affords a reliable measure of the end-point correction. H. I.

⁸⁸ *J. Amer. Chem. Soc.*, 1945, **67**, 1916.

⁸⁹ *Ibid.*, 1943, **65**, 1348; cf. R. Pasternak, *Helv. Chim. Acta*, 1948, **31**, 753.

⁹⁰ *Ind. Eng. Chem. Anal.*, 1944, **16**, 147.

⁹¹ *Ibid.*, 1945, **17**, 332.

⁹² *Anal. Chem.*, 1947, **19**, 675.

⁹³ *Ibid.*, p. 197.

⁹⁴ *J. Amer. Chem. Soc.*, 1948, **70**, 1047.

⁹⁵ D. P. Evans, *Analyst*, 1947, **72**, 99.

5. ANALYSIS OF SEA WATER.

There are present in the sea widely different concentrations of a large number of inorganic ions as well as colloidal and particulate inorganic and organic matter. Some fifty elements¹ have already been detected and the presence of others may be inferred from their occurrence in marine organisms.² Of the major elements present some (*e.g.*, sodium and potassium) are amongst the most difficult to determine, others (*e.g.*, calcium, strontium, and magnesium) are not easy to separate, and constituents of great biological importance (*e.g.*, phosphates and nitrates) are present in concentrations far below those normally dealt with by the microchemist, a few $\mu\text{g./l.}$ being of great importance. The high chloride-ion concentration and the salt content are constant complicating factors which often render modification of conventional methods essential.

The major constituents of the oceanic water bear a virtually constant ratio to the total salts, being unaffected by land drainage, so that except for special purposes the determination of more than one element is rarely made. It is usual to determine the silver-precipitated halides (chlorinity). An international standard for chlorinity independent of atomic weights has been maintained by referring all determinations to the so-called Copenhagen "Normal Water," which has been established as a permanent standard³ in terms of the mass of silver required to precipitate completely the halogen in one kg. of that water. Using recent values, J. Lyman and R. H. Fleming⁴ give values for the major constituents in terms of chlorinity and salinity.

The concentrations of other elements are affected by biological agencies, and for reason of space attention will be confined to a selection of the most important of these; the concentrations are expressed in units recommended by the Association D'Océanographie Physique,⁵ and approximate ranges are given for the elements considered. By drawing attention to the marine literature it is hoped to minimise the regrettable duplication of effort so noticeable in the analysis of nutrient materials such as phosphate and nitrate which are important in many biological and biochemical studies, and by concentrating on those elements present in minute concentration, the attention of physical chemists may be drawn to a field in which reaction kinetics at high dilution are of great importance.

Phosphorus and Arsenic.—*Phosphates* (0—0.003 mg.-atom of $\text{PO}_4\text{-P/l.}$). The earlier work⁶ involved either evaporation or precipitation with ferric salts.

¹ H. U. Sverdrup, M. W. Johnson, and R. H. Fleming, "The Oceans," New York, 1942.

² D. A. Webb, *Sci. Proc. Roy. Dublin Soc.*, 1937, **21**, 505.

³ J. P. Jacobsen and M. Knudsen, *Assoc. Oceanog. Physique, Publ. Sci.* No. 7, 1940.

⁴ *J. Marine Res.*, 1940, **3**, 134.

⁵ B. Holland-Hansen, J. P. Jacobsen, and T. G. Thompson, *Assoc. Oceanog. Physique, Publ. Sci.* No. 9, 1948.

⁶ D. J. Matthews, *J. Marine Biol. Assoc.*, 1916, **11**, 122; 1917, **11**, 251; E. Raben, *Wissenschaft. Meeresunters.*, 1916—1920, **18**, 1.

W. R. G. Atkins and E. G. Wilson⁷ were the first to apply the Denigès reaction and all subsequent work has been done using this method, a recent summary of which is given by R. J. Robinson and T. G. Thompson.⁸ Much work has been done on this method of determining phosphates, since the element is of great importance to many branches of biochemical work. However, a great deal of the work is repetitive and a fundamental study of the reactions and their kinetics is still required. A blue colour can be produced under the appropriate conditions by the action of many reducing agents upon the heteropoly-acids of molybdic and phosphoric acids and the intensity of the colour is dependent upon many variables, but for the quantities of phosphate occurring in sea water, only stannous chloride reaches the required sensitivity. K. Kalle's important studies,⁹ much of which were repeated by J. Tischer,¹⁰ show that the visual blue is affected by halides and the absorption in the violet is appreciably higher in sea water owing to the production of yellow tints in the formation of which molybdate, chloride, and bivalent tin ions are considered to be involved. L. H. N. Cooper¹¹ suggested that these yellow colours, particularly noticeable with excess of stannous chloride, are due to the formation of complex molybdenyl halides and their subsequent hydrolysis. When comparing the colour developed in sea water with standards made in distilled water it is necessary to apply a correction for the amount of salt, and since temperature affects the colour development, the sensitivity, and the salt error, both the standards and unknown should be at the same temperature. A special acid molybdate reagent being used, conditions were found under which the extinction was proportional to phosphate content and the salt error was minimal. It was found best to add the stannous chloride in two portions at an interval of 10 minutes, the intensity of colour being measured 5 minutes after the second addition. H. W. Harvey¹² has recently confirmed and extended these results.

Dissolved and particulate phosphorus (0—0.6 mg.-atom of P/l.). In addition to inorganic phosphate, dissolved organic phosphorus compounds are present as a result of organic decomposition. Complete oxidation of traces of organic matter in the presence of large quantities of salts, and the reduction of the arsenate formed from arsenite during this oxidation which is necessary in order to prevent its interference in the subsequent phosphorus determination, give rise to technical difficulties when only traces of organic phosphorus compounds are present. K. Kalle and also others¹³ found that the method developed for fresh waters¹⁴ were

⁷ *Biochem. J.*, 1926, **20**, 1223; *J. Marine Biol. Assoc.*, 1923, **13**, 119; 1925, **13**, 700.

⁸ *J. Marine Res.*, 1948, **7**, 33.

⁹ *Ann. Hydrog. Marit. Meteor.*, 1933, **61**, 124; *Ber. Deutsch. Wiss. Komm. Meeresforschung*, 1933, **6**, 273; *Ann. Hydrog. Marit. Meteor.*, 1932, **60**, 6; 1935, **63**, 58, 195.

¹⁰ *Z. Pflanz. Dung.*, 1934, **33**, 192.

¹¹ *J. Marine Biol. Assoc.*, 1938, **23**, 171.

¹² *Ibid.*, 1948, **27**, 337.

¹³ *Intern. Rev. ges. Hydrobiol.*, 1933, **29**, 221.

¹⁴ R. I. Robinson and G. Kemmerer, *Trans. Wiscon. Acad. Sci. Arts*, 1930, **25**, 117; L. Titus and V. W. Meloche, *ibid.*, 1931, **26**, 441.

unsatisfactory. E. Kreps and M. Osadchih¹³ used hydrogen peroxide in the oxidation, but Kalle considered that the danger due to production of organic acids (e.g., oxalic acid) which would interfere with the phosphorus determination renders this reagent unreliable. He therefore fumed the solid with sulphuric acid with the addition of a little copper salt. F. Berger,¹⁵ working on marine sediments, showed that Kalle's method did not give a complete oxidation, nor were persulphate and perhydrol completely effective; he recommends fuming nitric acid. Arsenic was not reduced by the earlier workers and Kalle used thiourea for this purpose, but L. H. N. Cooper¹⁶ had no success with this method of reduction.

A. C. Redfield, H. P. Smith, and B. H. Ketchum¹⁷ used a digestion similar to that of Kalle, but effected reduction of arsenate by prolonged heating with sulphite in stoppered bottles.

H. W. Harvey¹² has used an alternative method for determining the dissolved organic phosphorus in which considerable modifications are effected. The organic phosphorus compounds are hydrolysed with acid by autoclaving at 30–40 lb./sq. in. for 5–6 hours, sulphite being added to prevent oxidation of arsenite.

For the phosphorus determination in plankton, L. H. N. Cooper¹¹ found the methods developed by Robinson and Kemmerer¹⁴ and Titus and Meloche¹⁴ to be unsatisfactory owing to the difficulty of removing the last traces of the oxidising agent. Cooper used perhydrol and sulphuric acid, followed by the molybdenum-blue estimation, adding stannous chloride before the molybdate.

Arsenic (0.1–0.5 μ g.-atom of As/l). W. R. G. Atkins and E. G. Wilson¹⁸ suggested that the discrepancy between their results and those of D. J. Matthews,⁶ when compared with the values obtained by E. Raben⁶ on the phosphate content of sea water, were due to the fact that they used Denigès's colorimetric method and Matthews used the method of L. Pouget and D. Chouchak,¹⁹ whilst Raben's method involved evaporation with nitric acid. It is suggested that, as arsenic in sea water exists largely as arsenite, after oxidation (Raben) this would be included in the phosphate. Atkins and Wilson found that Pouget and Chouchak's method gives an immediate opalescence in the cold (if dilute, on standing) with phosphates, opalescence only on warming with an arsenate, and with arsenite only a faint opalescence on warming owing probably to oxidation to arsenate. They also showed that the Denigès reaction could be used for the determination of arsenate, but only a faint colour was produced with arsenites, again probably owing to oxidation.

N. W. Rakestraw and F. B. Lutz²⁰ used the Gutzeit method, and a modified Gutzeit method has been described²¹ which is essentially a modi-

¹³ *Intern. Rev. ges. Hydrobiol.*, 1938, **37**, 420.

¹⁴ *J. Marine Biol. Assoc.*, 1937, **21**, 673.

¹⁷ *Biol. Bull.*, 1937, **73**, 421.

¹⁵ *J. Marine Biol. Assoc.*, 1927, **14**, 609.

¹⁶ *Bull. Soc. chim.*, 1909, **5**, 104; 1911, **9**, 649.

²⁰ *Biol. Bull.*, 1933, **65**, 397.

²¹ S. Gorgy, N. W. Rakestraw, and D. L. Fox, *J. Marine Res.*, 1948, **7**, 22.

fication of that due to M. B. Jacobs and J. Nayler.²² After reduction of As^{v} by acid bisulphite, arsine was absorbed in sodium hypobromite and then reduced by hydrazine sulphate in the presence of acid molybdate. Arsenic (0.5 $\mu\text{g.}$ -atom/l.) present in the sea was fractionated into arsenite (50–60%), arsenate, dissolved organic arsenic, and particulate arsenic (each 8–16%).

Silicates (0.0007–0.14 mg.-atom of Si/l.).—W. R. G. Atkins and E. G. Wilson⁷ introduced the method of F. Diénert and F. Wandenbulcke,²³ using picric acid standards for the comparison, and further study of the reaction has been made by T. G. Thompson and H. G. Houlton²⁴ (*q.v.* for earlier references). The original picric acid standards were shown to be in error and corrections have been made.²⁵ The advantages of borax-buffered standards of potassium chromate²⁶ to replace picric acid have been stressed by R. J. Robinson and H. J. Spoor,²⁷ who found that the full colour development took place within 3 minutes and there was no fading within 2 hours. Temperature was found to be without effect. S. W. Brujewicz and L. K. Blinov's results²⁸ on the effect of salt concentration were not confirmed; they found a correction factor of 1.16 in contrast to the Russian workers' value of 1.66. Diénert and Wandenbulcke found that silica in the colloidal form is not determined by these reagents, but further investigations on this and upon the effect of salinity upon the colour development appear desirable.

Nitrogen.—*Ammonia* (0.35–3.5 mg.-atom of $\text{NH}_4\text{-N}$ /l.). H. E. Wirth and R. J. Robinson²⁹ have compared the earlier methods³⁰ and found all the reagents except Treadwell's to have a non-sensitive region. The sensitivity of Treadwell's reagent increases with increasing chlorinity, but Beer's law does not apply at low concentrations. A. Krogh³¹ used a vacuum-distillation method after making the water alkaline, the liberated ammonia being absorbed in hydrobromic acid and determined by T. Teorell's naphthyl-titration.³² Air at reduced pressure is used to drive off ammonia, and attention must be paid to blank determinations. The accuracy of a single determination is of the order of 0.04 $\mu\text{g.}$ of nitrogen (20-ml. sample). The method can be adapted for the determination of ammonia in air.

²² *Ind. Eng. Chem. Anal.*, 1942, **14**, 442; see also *Ann. Reports*, 1944, **41**, 282.

²³ *Compt. rend.*, 1923, **176**, 1478.

²⁴ *Ind. Eng. Chem. Anal.*, 1933, **5**, 417.

²⁵ E. J. King, *Contr. Canad. Biol. and Fish.*, 1931, **8**, 119; E. J. King and C. C. Lucas, *J. Amer. Chem. Soc.*, 1928, **50**, 2395; Robinson and Kemmerer, ref. 14, p. 129.

²⁶ H. W. Swank and M. G. Mellon, *Ind. Eng. Chem. Anal.*, 1934, **6**, 348.

²⁷ *Ibid.*, 1936, **8**, 455.

²⁸ *Bull. State Oceanog. Inst. U.S.S.R.*, 1933, No. 14, 44.

²⁹ *Ind. Eng. Chem. Anal.*, 1933, **5**, 293.

³⁰ R. Witting, *Oefv. Finska Vet.-Soc. Förh.*, 1915, **57**, No. 21; H. Wattenberg, *Cons. Perm. Intern. Rapp.*, 1929, **53**, 90; *Ann. Hydrog.*, 1931, **59**, 95; T. Braarud and A. Klem, *Healradets Skr.*, 1931, No. 1; L. H. N. Cooper, *J. Marine Biol. Assoc.*, 1933, **13**, 677; K. Buch, *Merentutkimuslaitoksen Julkaisri. Havs. Skrift.*, 1920, 2.

³¹ *Biol. Bull.*, 1934, **67**, 126.

³² *Biochem. Z.*, 1932, **248**, 246.

Nitrate (0.1—43.0 mg.-atom of $\text{NO}_3/\text{l.}$). The phenoldisulphonic acid method is not applicable in the presence of chloride. Reduction to ammonia has been used,³³ but the method is tedious and the results are open to question, since ammonia may be formed during reduction from nitrogenous substances. Two methods have been employed, both depending upon oxidation of a reagent in strong sulphuric acid with the production of coloured compounds. W. R. G. Atkins³⁴ proposed the use of diphenylbenzidine, but H. W. Harvey's reduced strychnine reagent³⁵ is more commonly employed; directions are given for preparing the reagent, the properties of which are somewhat capricious. The presence of much dissolved or particulate organic matter vitiates the results. Difficulties were reported by T. G. Thompson and M. W. Johnson,³⁶ but L. H. N. Cooper,³⁷ using safranin as an artificial standard, found the method satisfactory, although erratic results were obtained in the presence of nitrites. B. M. G. Zwicker and R. J. Robinson³⁸ confirmed by analysis that strychnidine and tetrahydrostrychnine were the main products in the reduction employed by Harvey and they suggest the use of strychnidine (which gives a more intense absorption maximum) prepared by electrolytic reduction of strychnine in sulphuric acid solution using a mercury cathode.³⁹ Data are given concerning the effect of reagent concentration on the colour produced with this strychnidine reagent. Distrychnidyl, although difficult to prepare and use, is twice as sensitive as the strychnidine reagent. Further details of the preparation of a satisfactory reagent and of its behaviour are given by W. A. Riddell⁴⁰ and D. Rochford,⁴¹ who recommend addition of hydrochloric acid to increase the sensitivity.

W. R. G. Atkins³⁴ (*q.v.* for earlier work) has determined the necessary conditions for the use of E. A. Letts and F. W. Rea's diphenylbenzidine reagent.⁴² Nitrites give erratic results. In view of the fact that it has been reported that the Harvey reagent and diphenylbenzidine reagent differ little in sensitivity, the neglect of the latter would hardly seem justified.

Dissolved organic nitrogen (0.1—10.0 mg.-atom of N/l.). The dissolved nitrogen in lake waters has been determined and fractionated into a number of components, samples obtained by evaporation of large quantities of water being used.⁴³ Amino- and non-amino-nitrogen were determined, but

³³ E. Raben, *Wiss. Meeresunters.*, 1905, **8**, 81; 1910, **11**, 303; 1914, **16**, 207.

³⁴ *J. Marine Biol. Assoc.*, 1932, **18**, 167.

³⁵ *Ibid.*, 1926, **14**, 71; 1928, **15**, 183.

³⁶ *Publ. Puget Sound Biol. Station*, 1929, **7**, 345.

³⁷ *J. Marine Biol. Assoc.*, 1932, **18**, 161. ³⁸ *J. Marine Res.*, 1944, **5**, 214.

³⁹ B. M. G. Zwicker and R. J. Robinson, *J. Amer. Chem. Soc.*, 1942, **64**, 790.

⁴⁰ *J. Biol. Bd. Canad.*, 1936, **2**, 1.

⁴¹ Commonwealth of Australia, C.S.I.R., Bull. No. 220, 1947.

⁴² *J.*, 1914, **105**, 1157.

⁴³ B. P. Domogalla, C. Juday, and W. H. Peterson, *J. Biol. Chem.*, 1925, **63**, 269; W. H. Peterson, E. B. Fred, and B. P. Domogalla, *ibid.*, p. 287; E. A. Birge and C. Juday, *Bull. Bur. Fisheries*, 1926, **42**, 185; E. A. Birge and C. Juday, *Proc. Nat. Acad. Sci.*, 1926, **12**, 515.

it is not certain that no decomposition had taken place during evaporation. The albuminoid and total nitrogen of water of the Puget Sound have been investigated by R. J. Robinson and H. E. Wirth,⁴⁴ using standard methods of analysis and large volumes of water. A. Krogh and A. Keys,⁴⁵ in developing a method for smaller quantities of water, abandoned Kjeldahl methods since ammonia was always obtained in amounts from 0.5 to 2 μ g. of nitrogen per ml. on heating sulphuric acid, and all efforts to remove this "organic N" failed. Their method (sensitivity approximately 0.3 μ g. of N) involves digestion of the sample at 500° with sodium hydroxide in a silver tube in an atmosphere of hydrogen. The ammonia formed is then taken up in N/100-hydrobromic acid, combined with sodium hypobromite and the excess hypobromite titrated according to Teorell's method (see p. 341). Details are given for purification of the hydrogen, setting up the apparatus, and preparation of distilled water free from organic nitrogen. T. von Brand and N. W. Rakestraw,⁴⁶ using the method, showed that the error is usually below 10% in samples containing approximately 200 μ g./litre of dissolved organic nitrogen.

Carbon.—*Dissolved and particulate carbon* (0.1–0.4 mg.-atom of C/l.). A number of methods involving alkaline permanganate have been used to determine the dissolved organic matter, but none can be considered very satisfactory.⁴⁷ A. Krogh and A. Keys⁴⁵ developed a wet combustion technique similar to that of H. Lieb and H. G. Krainich,⁴⁸ the method involving the removal of salts. After expulsion of carbon dioxide by boiling, most of the chloride is precipitated by thallium sulphate, and after evaporation, the dry residue is oxidised with a mixture of chromic and sulphuric acids in a current of carefully washed air. The carbon dioxide and carbon monoxide are carried through an oxidising combustion tube into baryta, the excess of which is titrated with hydrochloric acid. 25 ml. of water are used and careful attention to blanks is emphasised. The accuracy approaches 0.1 mg. of carbon/l. but the blank is rather high. By using filters, colloidal, soluble, and particulate carbon were differentiated.

Trace Metals.—Zinc can be determined with dithizone,⁴⁹ but before determination of manganese (as permanganate)⁵⁰ or iron (as the thiocyanate complex)⁵¹ halides and organic matter must be removed completely. N. W. Rakestraw, H. E. Mahneke, and E. F. Beach⁵² first concentrate the

⁴⁴ *J. du Cons.*, 1934, 9, 15, 187.

⁴⁵ *Biol. Bull.*, 1934, 67, 133.

⁴⁶ *J. Marine Res.*, 1941, 4, 76.

⁴⁷ W. R. G. Atkins, *J. Marine Biol. Assoc.*, 1922, 12, 772; 1923, 13, 160; G. J. Pereira, *Bol. de Pescas*, 1924, 9, 149; W. E. Adeney and B. B. Dawson, *Sci. Proc. Roy. Dublin Soc.*, 1926, 18, No. 17; O. G. Ibanez, *Notas y Resúmenes*, 1928, II, No. 26; P. Chauchard, *Compt. rend.*, 1932, 194, 1256; *Ann. Inst. Oceanog.*, 1935, 15, 329.

⁴⁸ *Mikrochem.*, 1931, 3, 367.

⁴⁹ K. Buch, *Finska Kem. Medd.*, 1944, Nos. 1–2, 25.

⁵⁰ T. G. Thompson and T. L. Wilson, *J. Amer. Chem. Soc.*, 1935, 57, 233.

⁵¹ T. G. Thompson and R. W. Bremner, *J. du Cons.*, 1935, 10, 39; T. G. Thompson, R. W. Bremner, and I. M. Jamieson, *Ind. Eng. Chem. Anal.*, 1932, 4, 288.

⁵² *Ibid.*, 1936, 8, 136.

iron in sea water by precipitation and reduction with ammonium sulphide, the co-precipitated basic magnesium salts acting as excellent carriers. Fluoride did not interfere with the recovery of 0.01—0.04 mg./l. The authors noted that ethylene glycol monobutyl ether had a stabilising influence on the red thiocyanate complex which they extracted with amyl alcohol: since it was stable to light but not to heat it was necessary to control the temperature before extraction.

2:2'-Dipyridyl and 2:2':2''-tripyridyl⁵³ were introduced into sea water analysis by L. H. N. Cooper,⁵⁴ and a careful study of the reaction between dipyridyl and iron at high dilutions of the latter by K. Buch⁵⁵ emphasises some of the difficulties likely to be encountered. Thus according to Cooper and J. H. Boxendale and P. George⁵⁶ only undissociated dipyridyl ($K_1 = 1-2 \times 10^{-10}$, $K_2 \sim 10^{-14}$) molecules enter the complex, so that both pH, neutral salts, and concentration of reagents affect the reaction. Theoretical calculations using data obtained by L. H. N. Cooper⁵⁷ and by P. A. Kriukov and G. P. Awesjewitsch⁵⁸ are given by Buch.

Copper has been determined by sodium diethyldithiocarbamate.⁵⁹ H. Barnes⁶⁰ has given methods for the determination of copper and mercury in sea water solutions in connection with anti-fouling investigations. Other workers on this problem have discussed the copper content of marine organisms and sea water and the relationship to toxicity.⁶¹ Since the work of H. F. Prytherch⁶² attention has been paid to the copper content of oysters and sea water under natural and artificial conditions. G. A. Riley⁶³ has used the carbamate reagent with estuarine waters, and K. Buch⁴⁹ gives a dithizone method in a paper which includes useful data on the extraction of copper and zinc dithizonates by different solvents at varying pH values of the solution.

H. B.

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H. IRVING.

L. LEYTON.

⁵³ *Ann. Reports*, 1945, **42**, 258.

⁵⁴ *Proc. Roy. Soc.*, 1935, **B**, **118**, 419.

⁵⁵ *Finska Kem. Medd.*, 1942, **51**, 22.

⁵⁶ *Nature*, 1948, **162**, 777.

⁵⁷ *Proc. Roy. Soc.*, 1937, **B**, **124**, 299.

⁵⁸ *Z. Electrochem.*, 1933, **39**, 884.

⁵⁹ W. R. G. Atkins, *J. Marine Biol. Assoc.*, 1932, **13**, 193; 1933, **19**, 63.

⁶⁰ *Ibid.*, 1946, **26**, 303.

⁶¹ G. L. Clarke, *Biol. Bull.*, 1947, **92**, 73; C. M. Weiss, *ibid.*, 1947, **93**, 56.

⁶² *Ecol. Monographs*, 1934, **4**, 47.

⁶³ *J. Marine Res.*, 1937, **1**, 60.

INDEX OF AUTHORS' NAMES.

- Abel, J. J., 283.
Ablondi, F., 222.
Abraham, E. P., 207, 208.
Abrams, R., 249.
Ackroyd, H., 245.
Acree, F., 164, 167, 169, 170.
Adam, N. K., 34.
Adams, R., 35, 201, 211, 314.
Adams, R. E., 142.
Adell, B., 113.
Adeney, W. E., 343.
Adkins, H., 134, 136, 199, 200.
Aeppli, O. T., 278.
Agar, J., 219.
Aggarwal, S. L., 111.
Ainley, A. D., 92.
Ajl, S. J., 266.
Akulov, N. S., 81.
Albert, P., 86.
Albertson, N. F., 131.
Alcalay, W., 312.
Aldrich, L. T., 85.
Alexa, V., 330.
Alexander, A. E., 42.
Alexander, E. R., 130.
Allen, A. O., 8, 17, 24, 52.
Allsopp, A., 278.
Allsopp, C. B., 23.
Alper, T., 25, 31.
Altman, K. I., 254, 256, 265.
Alyea, H. N., 21, 23, 68.
Amelin, A. G., 107.
Aminoff, D., 274, 281.
Amphlett, C. B., 116.
Amstein, E. H., 321.
Andersen, H. C., 65.
Anderson, A. B., 189.
Anderson, B. L., 16.
Anderson, H. H., 97.
Anderson, R. B., 60.
Anderson, R. C., 233.
Anderson, R. J., 292, 295, 297, 298, 299, 302, 311.
Anderson, T., 306.
Andersson, K. J. I., 284.
Anfinson, C. B., 241.
Angelescu, E., 42, 43.
Angier, R. B., 226, 227, 230, 231, 233, 237.
Anker, H. S., 241.
Anouar, M., 90.
Anslow, W. P., jun., 221.
Apin, A. J., 101.
Appel, W., 105.
Appleby, W. G., 60.
Appleyard, R. K., 8.
Arbusov, B. A., 128, 177.
Archer, S., 131.
Arden, T. V., 84, 271.
Arens, J. F., 204.
Aristoff, E. E., 137.
Armstrong, (Miss) G. P. 136.
Armstrong, M. D., 221.
Armstrong, W. D., 254, 267.
Arnell, J. C., 60.
Arnstein, H. R. V., 192.
Aronson, J. D., 299.
Arth, G. E., 223, 233.
Arthur, J. R., 95.
Artsdalen, E. R. van, 64, 65.
Arvidson, H., 246.
Ashmore, P. G., 74.
Ashworth, R. do B., 206.
Atherton, F. R., 138.
Atkins, W. R. G., 339, 340, 341, 342, 343, 344.
Atkinson, H. F., 272.
Attoe, O. J., 329.
Auclair, J. L., 274, 278.
Audrieth, L. F., 331.
Avakian, S., 212.
Avanoff, S., 113.
Avery, O. T., 298, 299.
Avery, W. H., 60.
Avramenko, L. L., 76.
Awesjewitsch, G. P., 344.
Aynsley, E. E., 105.
Babson, R. D., 219.
Bachmann, G. B., 125.
Bachmann, W. E., 137, 208, 209.
Backer, H. J., 236.
Backes, M., 207.
Bacon, R. G. R., 176, 177.
Baddiley, J., 138, 208.
Badger, G. M., 136.
Badin, E. J., 77.
Baer, E., 169.
Baget, J., 105.
Bagge, E., 13.
Baggenstoss, A. H., 293.
Baggesgaard-Rasmussen, H., 336.
Bahr, G., 107.
Bailar, J. C., 113.
Bailar, J. C., jun., 107.
Bailes, R. H., 84, 113.
Bair, R. K., 137.
Baird, W. S., 319.
Baker, B. R., 220, 221, 222, 223, 224.
Baker, L. E., 10.
Baker, P. B., 272, 273, 282.
Baker, W., 187, 207, 208.
Baker, W. E., 123.
Baldwin, E., 271, 277.
Bale, W. F., 259.
Balfour, W. M., 259.
Balz, G., 318, 319, 322.
Bamziger, N. C., 116.
Bandel, G., 335.
Bandler, M., 105.
Banerjee, P. C., 83.
Banks, C. K., 332.
Bardcen, J., 86.
Bardishev, I. I., 174.
Bardwell, D. C., 21, 22.
Barkelaw, C. H., 113.
Barker, B. I., 294.
Barker, F. G., 326.
Barker, H. A., 244, 252, 260.
Barker, R. L., 176, 178.
Bartrop, J. A., 189.
Barnes, F. W., 245.
Barnes, H., 344.
Barnes, R. A., 156.
Barnes, R. B., 328, 330.
Barrer, R. M., 61, 96.
Barron, E. S. G., 262.
Barrowcliff, M., 314.
Barry, V. C., 312, 314.
Barthel, W. F., 164, 165, 166, 167, 169, 170, 173.
Bartlett, P. D., 143, 145, 147.
Barton, D. H. R., 60, 149, 183, 184.
Barton, N., 193, 198.
Bartz, J. R., 308.
Basolo, F., 113.
Bassett, H., 82.
Bastiansen, O., 183.
Bateman, L., 114.
Bates, R. W., 285.
Baudisch, O., 137.
Baudouin, A., 331.
Bauer, R., 319.
Bauer, S. H., 92.
Baumeister, L., 23.
Bavel, T. van, 134.
Bawn, C. E. H., 23, 51.
Baxendale, J. H., 159, 344.
Baxter, R. A., 122, 214.
Beach, E. F., 343.
Beachell, H. C., 157.
Beck, M., 110.

- Becker, W. W., 333.
 Becquerel, J., 5.
 Beerwald, A., 319.
 Behrens, O. K., 212, 214.
 Belcher, R., 333.
 Beljakov, M. I., 107.
 Bell, D. J., 277.
 Bell, F., 196.
 Bell, G. H., 295.
 Bell, R. N., 101.
 Beloff, A., 241.
 Belt, M., 227.
 Belton, J. G., 312.
 Bénard, J., 86.
 Bender, H., 59.
 Bendich, A., 205, 246.
 Bendigo, B. B., 169.
 Benedétti-Pichler, A. A., 334.
 Benesi, H. A., 109.
 Benians, T. H. C., 299.
 Benkeser, R. A., 219.
 Benson, A. A., 276.
 Bentley, R., 208, 260, 261.
 Bergel, F., 207.
 Berger, F., 340.
 Berghe, J. van den, 211.
 Bergman, W. E., 101.
 Bergmann, E., 138.
 Bergmann, E. D., 132.
 Bergmann, F., 151.
 Bergstrand, H., 325.
 Bergström, S., 246.
 Berman, L., 215.
 Berman, S. M., 332.
 Bernal, J. D., 46.
 Bérnard, J. B., 112.
 Bernheim, F., 306, 309.
 Bernold, E., 186.
 Bernstein, S., 202, 221, 222, 223.
 Bernthsen, A., 207, 212.
 Berry, A. J., 331.
 Berry, J. W., 328, 330.
 Berry, T. M., 322.
 Berthelot, A., 310.
 Besson, J., 112.
 Bethe, H., 10.
 Beucker, H., 158.
 Bevington, J. C., 101.
 Bhattacharya, B. K., 182.
 Billen, G. N., 135.
 Billica, H. R., 199.
 Bingley, J. B., 108.
 Birch, A. J., 99.
 Birckenbach, L., 101.
 Birge, E. A., 342.
 Birkinshaw, J. H., 188.
 Bishop, W. B. S., 22.
 Bitskei, J., 332.
 Blackburn, S., 276, 278.
 Blair, V. E., 281.
 Blanchard, M. H., 288.
 Blass, J., 272.
 Blicke, F. F., 206.
 Blinov, L. K., 341.
 Bloch, F., 10, 14.
 Bloch, I., 213.
 Bloch, K., 240, 241, 245, 253, 262, 263, 297.
 Block, R. J., 274, 275, 280.
 Blocker, J. M., jun., 98.
 Blomquist, A. T., 127.
 Bloom, E. S., 229.
 Bloom, H., 87.
 Blumberg, E. A., 59.
 Blumrich, K., 335.
 Bodart, J., 16.
 Bode, H., 102.
 Bodenstein, M., 54, 55, 65.
 Boeknoogen, H. A., 207.
 Boesken, J., 141.
 Boeters, O., 137.
 Boettner, E. A., 323.
 Bogdandy, S. von, 69.
 Bohme, H., 105.
 Bohonos, N., 229.
 Bohr, N., 10.
 Boissevain, C. H., 297.
 Boldingh, J., 270, 282.
 Bolman, O. E. A., 38.
 Bolz, A., 93.
 Bond, A. C., 122.
 Bondi, A., 138.
 Bonet-Maury, P., 6, 23, 24.
 Bonhoeffer, K., 16.
 Bonso, O., 127.
 Boon, S. D., 327.
 Boon, W. R., 277.
 Booth, H. S., 102, 109, 116.
 Boothe, J. H., 226, 227, 230, 231, 233, 237.
 Boquet, A., 300, 301.
 Boratynski, K., 328.
 Bordwell, F. G., 137.
 Bornstein, B. T., 260.
 Borsche, W., 196.
 Borsook, H., 276.
 Boscott, R. J., 270.
 Bosworth, R. C. L., 99.
 Botty, M. C., 275.
 Bouckaert, J. P., 283.
 Bougault, J., 198.
 Boullé, A., 101.
 Bourquin, J. P., 200.
 Bowden, K., 134.
 Bowman, R. E., 129.
 Braarud, T., 341.
 Brackebusch, H., 319.
 Bradbury, N. E., 14.
 Brady, A. P., 38.
 Bragg, Sir W., 11.
 Bramley, G. E. A., 317.
 Branchen, L. E., 336.
 Brand, E., 268, 286, 287.
 Brand, T. von, 343.
 Brandt, C. W., 180, 182.
 Brasseur, P., 112.
 Brattain, K. G., 19.
 Brattain, W. H., 86.
 Braudo, C., 322.
 Brauer, G., 103.
 Brauer, W., 319.
 Braun, J. von, 198.
 Bray, J. M., 325.
 Braz, G. I., 218.
 Breckenridge, J. G., 88.
 Brederode, H. V., 96.
 Breger, I. A., 6.
 Brehm, W. J., 202.
 Breit, J. E., 332.
 Breitweiser, W., 327.
 Bremner, R. W., 343.
 Brennan, E. A., 176, 177.
 Brønneisen, E., 217.
 Bretey, J., 310.
 Bretschger, M. E., 104.
 Brewer, A. K., 91.
 Brewington, G. P., 323.
 Brigando, (Mlle.) J., 113.
 Briggs, F., 196.
 Brink, N. G., 202, 308.
 Brintzinger, H., 85.
 Briscoe, H. V. A., 92.
 Brocard, J., 90.
 Broda, E., 23.
 Brode, W. R., 316, 325.
 Brodersen, P. H., 109.
 Brodrick, C. I., 207, 210.
 Brody, J. K., 325.
 Broglin, J., 98.
 Brommelle, N. S., 319.
 Brosset, C., 108.
 Brouns, R. J., 113.
 Brown, D. J., 145.
 Brown, F., 273, 298.
 Brown, F. B., 54, 55.
 Brown, G. B., 205, 221, 246, 250, 251.
 Brown, H. A., 308.
 Brown, H. C., 93.
 Brown, J. B., 112.
 Brown, R., 130.
 Brown, R. H., 335.
 Brown, R. K., 158.
 Brown, W. G., 122.
 Brown, W. W., 319.
 Brownlee, G., 293, 300, 302, 304, 306.
 Brownscombe, F. R., 24.
 Brujewicz, S. W., 341.
 Bruni, G., 213.
 Brunstetter, B. C., 325.
 Brus, G., 174.
 Bruson, H. A., 124, 125.
 Bruschy, F. J., 200.
 Bruun, T., 180.
 Bryan, F. R., 323.
 Buch, K., 341, 343, 344.
 Buchanan, G. L., 193, 198.
 Buchanan, J. M., 247.
 Buchheit, P., 93.
 Buchholz, E., 102.
 Buchman, E. R., 156, 214.
 Büchi, G., 176, 186.
 Büchi, J., 309.
 Buehler, C. A., 186.

- Bugge, G., 213.
 Bugie, E., 307.
 Bullock, J. K., 294.
 Burton, C. A., 149.
 Burcham, W. E., 16.
 Burgener, J. E., 317.
 Burke, H. E., 294.
 Burns, W., 116.
 Bursian, K., 191.
 Burstall, F. H., 84, 271, 283.
 Burton, C. J., 275.
 Burton, M., 10, 17, 52.
 Burton, V. L., 6.
 Bury, C. R., 50.
 Bustinza, F., 312.
 Buston, H. W., 313.
 Butler, G. C., 301.
 Butler, J. A. V., 289.
 Butler, S. M. J., 331.
 Buttle, G. A. H., 305.
 Butts, P. G., 333.
 Buyanov, N. V., 317.
 Byé, J., 108.
 Byers, L. W., 309.
 Cady, G. H., 86, 109.
 Caillat, R., 96.
 Caillot, T., 24.
 Cain, C. K., 233, 234, 236.
 Cairns, T. L., 217.
 Calam, C. T., 277.
 Caldecourt, V. J., 319, 322, 323.
 Calfee, R. K., 330.
 Calhoun, G. M., 55.
 Calker, J. van, 317, 325.
 Callen, J. E., 218.
 Calloman, F. T., 305, 306.
 Callon, K. W., 317.
 Callow, R. K., 309.
 Calmette, A., 300.
 Calmont, P., 10.
 Calvin, M., 84, 113, 212, 276.
 Cameron, A. T., 7.
 Campaigne, E., 201, 211.
 Campbell, A. N., 88.
 Campbell, B. K., 217, 218.
 Campbell, I. E., 98.
 Campbell, I. G. M., 172.
 Campbell, K. N., 217, 218.
 Campbell, N., 216.
 Campbell, W. P., 176, 180, 181, 182.
 Capron, P. C., 6, 19, 20.
 Caraway, K. P., 333.
 Cardon, B. P., 244.
 Carless, C. M., 318.
 Carlsson, C. G., 325.
 Carmack, M., 211, 212.
 Carmody, W. R., 331.
 Carpeni, G., 97, 108.
 Carr, D. T., 308.
 Carr, F. H., 291.
 Carrière, E., 86, 87, 90, 91, 94, 103.
 Carter, H. E., 309.
 Casarett, G. W., 254.
 Cass, W. E., 143, 145.
 Catch, J. R., 130, 208, 269, 275, 277.
 Cattelain, E., 198.
 Cauchois, (Mlle.) Y., 107.
 Caughlan, J. A., 219.
 Cavalea, L., 89, 90.
 Cavalieri, L. F., 251.
 Cecconi, R., 89.
 Ceithaml, J., 267.
 Cerenkov, P. A., 16.
 Chabrier, P., 199.
 Chaïet, L., 231.
 Chain, E., 207, 208.
 Chamberlin, E. M., 142.
 Chambers, A. R., 188.
 Chantrenne, H., 242.
 Chapman, N. B., 138.
 Chappell, D. G., 330.
 Chaput, E. P., 217.
 Chard, S. J., 136.
 Chargaff, E., 250, 274, 275, 281.
 Charles, A. F., 290.
 Charpy, A., 313.
 Chattaway, F. W., 226.
 Chatterjee, R., 216.
 Chauchard, P., 343.
 Chaudron, G., 112.
 Chemerda, J. M., 137.
 Chénicek, J. A., 159.
 Cherbuliez, E., 128.
 Chibnall, A. C., 284, 287.
 Cholak, J., 321, 325.
 Choppin, A. R., 60.
 Chorine, V., 310.
 Chouchak, D., 340.
 Chow, B. F., 289.
 Chrétien, A., 89, 98, 110.
 Christ, C. L., 275.
 Christiansen, J., 41.
 Christine, O. W., 317.
 Churchill, H. V., 320.
 Churchill, J. R., 320, 325.
 Ciapetta, F. G., 331.
 Cirilli, V., 90.
 Claesson, S., 269.
 Clapp, L. B., 218.
 Clapper, W. E., 260.
 Clark, R. H., 125.
 Clarke, B. L., 324.
 Clarke, G. L., 344.
 Clarke, H. T., 200.
 Clay, A. C., 306.
 Clay, M. G., 306.
 Clayton, H. R., 318, 319, 322, 326.
 Clemo, G. R., 178.
 Cloetens, R., 19, 21.
 Clough, G. W., 199.
 Clusius, K., 97, 110.
 Clutton, R. F., 301.
 Coates, A. C., 321.
 Cockburn, R., 278.
 Coffin, C. C., 60.
 Coghill, 298.
 Cohen, A., 192, 194.
 Cohen, P., 317.
 Cohen, P. P., 242, 252.
 Cohn, E. J., 288.
 Cole, Q. F., 205.
 Coleman, A. L., 218.
 Coleman, G. H., 212, 314.
 Coleman, P. D., 323.
 Collins, C. B., 92.
 Collins, G. B., 16.
 Collins, H. L., 317.
 Collinson, E., 27, 31.
 Collit, G. B., 302.
 Colman, G. H., 35.
 Colwell, 30.
 Compere, E. L., 60.
 Conalty, M. L., 312.
 Conant, J. B., 335.
 Condike, G. F., 93.
 Condon, E. U., 14.
 Conn, J. B., 231.
 Conrad, N., 132.
 Conroy, H. W., 331.
 Consden, R., 268, 270, 272, 273, 274, 276, 278, 279, 283.
 Controulis, J., 308.
 Convey, J., 326.
 Cook, A. H., 130, 200, 206, 207, 208, 209, 214, 216, 269, 277.
 Cook, J. W., 136, 192, 193, 194, 195, 196, 198.
 Cook, R. P., 105, 314.
 Cook, W. B., 159.
 Cookson, R. C., 126.
 Coolidge, W. D., 7.
 Cooper, F. S., 7.
 Cooper, H., 304.
 Cooper, L. H. N., 339, 340, 341, 342, 344.
 Corner, E. S., 57.
 Cornu, A., 317.
 Correll, H., 317.
 Corriez, P., 102.
 Corrin, M. L., 38, 42, 44, 47.
 Corse, J. W., 212.
 Corte, H., 85.
 Cory, J. C., 97.
 Cosulich, D. B., 226, 227, 233.
 Cottin, M., 104.
 Cottle, D. L., 106.
 Coulthard, C. E., 297, 298.
 Courty, C., 99.
 Cowley, J. M., 93.
 Cox, E. G., 106.
 Cox, R. F. B., 178.
 Craig, L. C., 279.
 Crammer, J. L., 274, 282.
 Cranshaw, T. E., 116.
 Crawford, B. L., 114.
 Crawford, M., 87.

- Creighton, M. M., 297.
 Criegee, R., 158, 198.
 Crist, R. H., 52, 54, 55.
 Crombie, L., 169, 171, 173.
 Cromwell, N. H., 219, 220.
 Cronheim, G., 137.
 Crooks, H. M., 308.
 Crossbie, A. W., 136.
 Crossley, F. S., 129.
 Crosswhite, H. M., 323, 324.
 Crounse, N. N., 219.
 Crovath, A. M., 14.
 Crowder, J. A., 311.
 Crowfoot, D., 284.
 Croxton, F. C., 116.
 Cruickshank, D. B., 91.
 Crumpler, H. R., 275.
 Cruz, W. O., 259.
 Cueillon, J., 83, 86.
 Culhane, K., 291.
 Cullinane, N. M., 136.
 Cullis, C. F., 69, 74.
 Cultrera, R., 99.
 Cunneen, J. I., 154.
 Cunningham, G. L., 332.
 Curd, F. H. S., 215.
 Cuthbertson, W. F. J., 275, 282.
 Czarnetzky, E. J., 294.
 Dacey, J. R., 60.
 Dainton, F. S., 8, 10, 14, 16, 18, 24, 27, 30, 31, 69, 74, 77, 101, 159.
 Daizins, E., 310.
 Dakin, H. D., 131.
 Dale, W. M., 25.
 Dam, H., 311.
 Danders, C., 97.
 Daniel, L. J., 233.
 Daniels, F., 55, 56.
 Dannley, R. L., 141.
 Darmon, S. E., 276, 287.
 Darzens, G., 123.
 Datar, D. S., 107.
 Dauben, H. J., jun., 169.
 Dauben, W. G., 142, 212.
 Daudel, R., 110.
 Daunt, J. G., 85.
 Davidson, A. E., 110, 111.
 Davidson, J. N., 278.
 Davidson, N., 13.
 Davidson, W. M., 165.
 Davies, D. G., 50.
 Davies, G. R., 84, 271, 283.
 Davies, W. D., 127.
 Davis, A. K., 329.
 Davis, C. H., 211.
 Davis, L. W., 98.
 Davis, T. W., 52.
 Davoud, J. G., 58.
 Dawes, E. A., 279.
 Dawson, B. B., 343.
 Dawson, I. M., 105.
 Dawson, J., 279.
 Deal, E. C., 332.
 Dean, H. F., 189.
 Dean, P. M., 212.
 Deasy, C. L., 276.
 De Boer, H., 103.
 De Boer, J. H., 88.
 De Duve, C., 283.
 Dehn, W. M., 189.
 Deinnes, L., 299.
 Delluva, A. M., 247, 267.
 Delwaulle, (Mlle.) M. L., 102.
 De Mende, S., 91.
 Dement, J., 82.
 Demers, P., 116.
 Dent, C. E., 268, 273, 274, 275, 278, 279, 282.
 Dervichian, D. G., 45, 46, 49.
 Desch, C. H., 84.
 DeTar, D. F., 154, 211, 212.
 De Vault, D., 268.
 Devos, C., 22.
 De Walt, C. W., 202.
 Dewar, M. J. S., 103, 114, 187, 192.
 Dewing, T., 305.
 DeWitt, T. W., 101.
 Dexter, S., 324.
 Dhingra, D. R., 155.
 Diamond, L. K., 233.
 Dick, A. T., 108.
 Dickens, F., 260.
 Dickenson, L., 297, 298.
 Dickson, G. T., 195, 196, 198.
 Diczfalussy, E., 307.
 Diehl, H., 113.
 Dieke, G. H., 323, 324.
 Diénert, F., 341.
 Dietert, H. W., 319, 320, 322, 323, 326.
 Di Fonzo, M., 307.
 Dirscherl, W., 290.
 Dittrich, C. W., 101.
 Djerassi, C., 156.
 Doak, G. O., 102.
 Doan, C. A., 292, 297, 298.
 Dobriner, K., 257.
 Dobson, F., 272, 273, 282.
 Dodds, E. C., 289.
 Dodonov, J. J., 97.
 Dolby, D. E., 226.
 Domagk, G., 305.
 Domange, L., 109.
 Dominé-Bergès, (Mme.) M., 101.
 Domingo, W. R., 328.
 Domogalla, B. P., 342.
 Donohue, J., 105.
 Donovan, R., 308.
 Dorfman, A., 262.
 Dorfman, E., 156.
 Dorfmann, L., 202, 223.
 Dorp, D. A. van, 204.
 Doucet, Y., 108.
 Dowling, G. B., 313.
 Drake, B., 272.
 Drake, H. C., 82.
 Drake, N. L., 198.
 Drew, R., 278.
 Druce, J. G. F., 82.
 Drucker, B., 278.
 Duane, W., 21, 23.
 Dubnikov, L. M., 109.
 Dubois, J. E., 124.
 Dubois, S., 103, 109.
 Dubos, R. J., 303, 304.
 Du Brow, P. L., 37.
 Duca, C. J., 310.
 Ducret, L., 103.
 Dudley, H. W., 298.
 Dürst, O., 176, 186.
 Dufay, J., 94.
 Duffield, R. B., 84.
 Dufraisie, C., 105.
 Dugger, B. M., 5.
 Duguet, R., 87.
 Duke, F. R., 333.
 Dunkin, G. W., 311.
 Dunstan, W. J., 157.
 Du Pont, A., 135.
 Durand, R., 44.
 Dustin, P., 190.
 Du Vigneaud, V., 199, 209, 214, 252, 283, 285, 286, 290.
 Dwyer, F. J. P., 113, 115.
 Dyke, H. B. van, 289.
 Eager, R. L., 110.
 Eakin, R. E., 233, 250.
 Eastcott, E. V., 313.
 Eastmond, E. J., 318.
 Eble, T. E., 277.
 Echols, L. S., 59.
 Ecker, E. E., 301.
 Eddy, C. A., 285.
 Edens, C. O., 297.
 Edison, A. O., 308.
 Edman, P., 278.
 Edsall, J. T., 268, 291.
 Edwards, J. W., 239.
 Egan, E. P., jun., 99.
 Egerton, (Sir) A. C., 77, 104.
 Eggenberger, D. N., 37.
 Ehmann, L., 156.
 Ehrensward, G. C. H., 213, 243.
 Ehrlich, J., 331.
 Ehrlich, P., 89.
 Eichel, H., 290.
 Eidinoff, M. L., 86.
 Eigen, E., 274, 275, 282.
 Eigsti, O. J., 190.
 Elbe, G. von, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77.
 Eley, D. D., 61.
 Eliasson, N. A., 246.
 Eliot, G. B., 234.
 Elks, J., 215.
 Elledge, B. E., 325.
 Elliot, D. F., 208.

Elliot, J. H., 336.
 Elliott, M., 166, 169, 173.
 Elliott, N., 116.
 Elliott, R. C., 269.
 Ellis, D., 195.
 Ella, V. R., 324.
 Elmore, K. L., 94.
 Elsdon, S. R., 252, 277.
 Elson, L. A., 92.
 Eltenton, G. C., 61.
 Elvidge, J. A., 207, 208, 209.
 Emanuel, N. M., 77, 79, 80.
 Emeléus, H. J., 60, 96.
 Emerson, W. S., 159.
 Emmart, E. W., 306, 310.
 Englis, D. T., 319.
 English, A. C., 116.
 English, J., 135.
 English, J. P., 205.
 Engström, A., 275.
 Engstrom, R. W., 323.
 Ensslin, F., 94.
 Epstein, J., 337.
 Epstein, S., 85.
 Erämetsä, O., 88, 91.
 Erbacher, O., 110.
 Erchak, M., jun., 90.
 Erden, B., 235.
 Erdtman, H., 189.
 Erickson, A. E., 236.
 Erickson, P. T., 314.
 Erlenmeyer, H., 205, 307.
 Errera, M., 256.
 Escolar, J. G., 331.
 Essex, H., 15, 19.
 Eucken, A., 103.
 Evans, D. P., 337.
 Evans, E. A., 252, 265, 288.
 Evans, M. G., 30, 61, 106, 159.
 Evans, T. W., 149, 189.
 Evans, W. C., 278.
 Evenson, O. L., 333.
 Everett, A. J., 149.
 Evers, E. C., 38.
 Ewens, R. V. G., 82, 83.
 Ewing, D. T., 325.
 Ewing, F. J., 84.
 Eyer, H., 290.
 Eyring, H., 20, 21, 22, 63.
 Faget, G. H., 314.
 Fahrenbach, M. J., 226, 227.
 Fairbrother, F., 111.
 Falkovsky, V. B., 58.
 Fanelli, R., 104.
 Fankuch, I., 90.
 Fano, U., 13.
 Fanta, P. E., 194, 198.
 Faraday Society, 114, 139.
 Farber, G., 97.
 Farber, S., 233.
 Farkas, A., 20.
 Farkas, L., 77.
 Farmer, E. H., 149, 201.

Farmer, T. H., 279.
 Farnworth, A. J., 157.
 Farrington, P. S., 334.
 Faure, P., 94.
 Feather, N., 83.
 Feenberg, E., 19.
 Fehér, F., 105.
 Feigl, F., 85, 94.
 Feitknecht, W., 91.
 Feldman, W. H., 293, 303, 305, 306, 307, 308, 310.
 Fellows, C. H., 22.
 Felton, L. D., 299.
 Fentress, J., 94.
 Fernelius, W. C., 82.
 Fernholz, H., 196.
 Ferrari, A., 89, 90.
 Ferrel, R. E., 291.
 Ferry, J. D., 288.
 Feussner, O., 322.
 Field, M. C., 37.
 Fieldes, M., 320.
 Fieser, L. F., 142, 176, 180, 182.
 Fildes, P., 302.
 Fill, M. A., 333, 334.
 Finholt, A. E., 122.
 Fink, E., 255.
 Fink, K., 275.
 Fink, R. M., 275.
 Finke, W. W., 83.
 Finland, M., 309.
 Fischback, H., 277.
 Fischer, E., 280.
 Fischer, H., 255.
 Fischer, W., 98.
 Fishel, W. P., 111.
 Fisher, A. M., 288, 290.
 Fisher, E., 88.
 Fisher, F., 153.
 Fisher, R. B., 280.
 Fitch, A., 290.
 Fitz, E. J., 320.
 Fitzgerald, R. J., 309.
 Flatt, R., 333.
 Fleck, E. E., 174, 176, 177, 178, 179.
 Fleming, R. H., 338.
 Fleming, T., 332.
 Fletcher, C. J. M., 52.
 Fletcher, R. G., jun., 203.
 Flood, A. E., 281.
 Florcy, K., 268.
 Flynn, E. H., 202.
 Foëx, M., 115.
 Folch, J., 313.
 Folkers, K., 124, 199, 200, 202, 214, 223, 233, 308.
 Folkins, H. O., 58.
 Folmer, H., 6.
 Fones, W. S., 128.
 Fonken, G. S., 199.
 Forbes, G. S., 97.
 Foreman, E. M., 274.
 Forkner, C. E., 297, 298.
 Forrest, H. S., 228, 236.

Forsén, L., 89.
 Forsyth, J. S. A., 59.
 Forsyth, W. G. C., 274, 281.
 Foster, G. E., 305.
 Foster, J. W., 231.
 Fouasson, F., 106, 107.
 Fowler, R. H., 56.
 Fox, C. L., 250.
 Fox, D. L., 340.
 Fox, G. W., 324.
 Fox, R. E., 14.
 Fraenkel-Conrat, H., 283, 291.
 Francis, J., 311.
 Franck, J., 17, 85.
 François, F., 102.
 Frank, F. C., 83.
 Frank, H. R., 194, 198.
 Frank-Kamenetsky, A. A., 81.
 Frank-Kamenetsky, D. A., 59.
 Franklin, A. L., 227.
 Fred, E. B., 342.
 Freeman, H. W., 82.
 Freiman, M., 152.
 French, D., 291.
 Freudenberg, K., 290.
 Freund, H., 98.
 Freund, R., 300.
 Freundlich, H., 41.
 Frey, (Mme.) H., 108.
 Frey, J. M., 174.
 Fricko, H., 23, 24, 25, 30.
 Friedberg, F., 242.
 Friedheim, G., 110.
 Friedmann, R., 302.
 Frisch, P., 105.
 Frost, A. A., 68.
 Frost, B. M., 308.
 Frudley, T. W., 135.
 Fuchs, C. F., 154, 160.
 Fürth, R., 319.
 Fugassi, P., 60, 63.
 Fujitani, J., 163, 172.
 Fukuri, G., 180.
 Fuller, A. T., 291.
 Funk, H., 85.
 Gabriel, S., 218.
 Gall, J. F., 278.
 Gallagher, T. F., 283.
 Gallais, F., 87, 88.
 Gallin, (Mlle.) G., 99.
 Galmiche, P., 110.
 Gardner, L. U., 293.
 Gardner, T. S., 216.
 Garkuscha, G. A., 174.
 Garlet, R., 99.
 Garner, C. S., 82.
 Garner, W. E., 19.
 Garrett, A. B., 116.
 Garrett, H. E., 39.
 Garrison, W. M., 23.
 Garstang, W. L., 69.
 Garvey, B. S., 158.

- Gaskin, J. G. N., 89.
 Gatewood, E. S., 207.
 Gatterer, A., 319.
 Gaudin, O., 165.
 Gaudry, R., 126, 279.
 Gaydon, A. G., 76.
 Gazzola, A. L., 231.
 Gedye, G. R., 19.
 Gee, E. A., 98.
 Geiling, E. M. K., 285.
 Gelat, A., 131, 132.
 Gelber, W., 91.
 Gelissen, H., 141.
 Geller, R. F., 99.
 Genger, L. G., 297.
 George, P., 59, 344.
 Gerbault, (Mlle.) M., 87, 90, 91.
 Gerbes, W., 12.
 Gerding, H., 96, 104.
 Gergely, J., 106.
 Gerlogh, T. D., 285.
 Gersdorff, W. A., 165, 171, 173.
 Gesser, F., 106.
 Getler, H., 250.
 Getz, C. A., 332.
 Ghiorso, A., 116.
 Gibson, N. A., 113.
 Giella, M., 131.
 Giesecke, F., 327.
 Gilbert, H. N., 86.
 Gillam, A. E., 165, 167, 172.
 Gillerot, R., 19.
 Gilman, H., 212, 219.
 Gimmingham, C. T., 173.
 Gingras, R., 279.
 Ginsberg, A., 136.
 Ginsberg, H., 201.
 Girard, A., 189.
 Given, P. H., 129, 135.
 Gladstone, M. T., 140.
 Glavind, J., 311.
 Glemser, O., 96.
 Glendenin, L. E., 83.
 Glendenning, M. B., 291.
 Glocker, R., 23.
 Glocker, C., 6, 9, 14, 22.
 Glover, R. E., 300, 305, 309.
 Glückauf, E., 85, 268, 269.
 Goebel, W. F., 299, 302.
 Goehring, M., 105, 106.
 Goeppe, R. M., jun., 203.
 Götsky, S., 21.
 Goldberg, A. A., 208, 313.
 Goldberg, G. M., 156.
 Goldberg, M. W., 207.
 Goldsmith, J. R., 90.
 Goldstein, M., 215.
 Goldstone, N. I., 332.
 Gollub, M. C., 266, 267.
 Gonick, E., 37, 50.
 Gonser, B. W., 98.
 Gonzalez Barredo, 334.
 Good, P. M., 274, 282.
 Goodall, R. R., 270, 272, 273, 275, 282.
 Goodson, L. H., 129.
 Goodwin, R. A., 324.
 Gordon, A. H., 270, 271, 272, 273, 274, 276, 278, 279, 283.
 Gordon, M., 233.
 Gorgy, S., 340.
 Gornall, F. H., 314.
 Goubreau, J., 93, 94.
 Gould, R. G., 267.
 Goy, S., 327.
 Gradsten, M. A., 128.
 Gränacher, C., 215.
 Graessle, O. E., 308.
 Graham, A. R., 130.
 Graham, W., 193.
 Graner, F., 103.
 Grant, G. H., 71.
 Gray, L. H., 6, 9, 12, 25.
 Green, A. A., 40.
 Green, A. F., 306.
 Green, C., 274.
 Green, D. E., 244.
 Green, N., 171, 173.
 Green, R. G., 173.
 Greenberg, D. M., 242, 243, 291.
 Greenberg, G. R., 250.
 Greenstein, J. P., 256.
 Greenwald, I., 90.
 Greep, R. O., 289.
 Greer, C. M., 35, 314.
 Gregor, U., 100.
 Gregory, J. D., 135, 279.
 Greinacher, H., 16.
 Grenall, A., 116.
 Grenberg, A. A., 114.
 Grewe, R., 192, 196.
 Grieger, P. F., 39.
 Griebel, W., 128.
 Griffith, A. S., 300.
 Griffith, R. L., 88.
 Griggs, M. A., 325.
 Grillot, E., 98.
 Grimm, H. H., 323.
 Grindley, J., 50.
 Grinstein, M., 254.
 Gripenberg, J., 189.
 Grisolia, S., 262, 265, 266.
 Grjébine, T., 83.
 Grønvold, F., 116.
 Gronwall, A., 312.
 Gross, A., 102.
 Gross, N. H., 264.
 Grove, D. H., 136.
 Grussner, A., 200.
 Gudgeon, H., 277.
 Günther, P., 19, 21, 23, 24.
 Guerin, H., 86.
 Guggenheim, E. A., 56.
 Guirard, B. M., 262.
 Guiter, H., 86, 87, 90, 91, 103, 108, 117.
 Gundermann, J., 44.
 Gurland, J., 98.
 Guseva, A. P., 256.
 Guss, C. O., 303, 310.
 Gutfreund, H., 284.
 Guthrie, F. C., 333.
 Haagen-Smit, A. J., 276.
 Haach, C. C., 113.
 Haackspill, L., 89, 90.
 Hadfield, (Miss) I. H., 334.
 Hänsner, V., 96.
 Hagemann, F., 116.
 Hagen, S. K., 103.
 Hahn, P. F., 259.
 Hais, M., 267.
 Haissinsky, M., 19, 104.
 Halberstadt, E. S., 149.
 Hald, P. M., 329.
 Halder, B. C., 91.
 Halevy, A., 151.
 Hall, D. A., 226.
 Hall, N. F., 335.
 Hall, R. T., 336.
 Haller, H. L., 164, 165, 166, 167, 169, 170, 172, 173.
 Halls, E. E., 89.
 Halsall, T. G., 281.
 Hammarsten, E., 246, 249.
 Hammick, D. Ll., 129, 135, 136.
 Hampton, B. L., 178.
 Hanby, W. E., 277.
 Hanford, W. E., 151.
 Hansley, V. L., 123.
 Happold, F. C., 226, 279.
 Hardegger, E., 204.
 Harding, W. M., 233.
 Hargreaves, G. H., 123.
 Harington, (Sir) C., 214, 291, 301.
 Hark, O. L., 113.
 Harker, D., 92.
 Harker, G., 22.
 Harkins, W. D., 38, 40, 41, 42, 44, 47, 48, 49, 50.
 Harmon, J., 151.
 Haroldson, H., 116.
 Harper, D. A., 325.
 Harper, S. H., 166, 169, 171, 172, 173.
 Harrad, G. J., 105.
 Harris, C. E., 219.
 Harris, G. A., 179, 180.
 Harris, G. C., 174, 175.
 Harris, G. M., 58, 95.
 Harris, I., 158.
 Harris, R., 271.
 Harris, S. A., 199, 223, 233.
 Harrison, G. C., 113.
 Harrison, H. C., 320.
 Harrison, J. A., 325.
 Hart, E. J., 24, 25.
 Hart, P. D., 304, 309.
 Harteck, P., 77.
 Hartford, W. H., 89.
 Hartley, F. R., 115.

- Hartley, G. S., 34, 35, 36,
 39, 41, 42, 47, 49.
 Hartman, P. F., 144.
 Hartough, H. D., 129, 136.
 Hartzell, A., 165.
 Harvey, H. W., 339, 340,
 342.
 Harvey, J. A., 116.
 Harwood, M. G., 90.
 Haslam, H., 335.
 Hasler, M. F., 322, 323.
 Hassel, O., 183.
 Hasselstrom, T., 175, 176,
 177, 178.
 Hastings, A. B., 241, 267.
 Hatfield, J. D., 94.
 Haugaard, G., 270.
 Hauptmann, H., 201.
 Hauser, C. R., 129.
 Hauser, E. A., 45.
 Hawkins, F., 312.
 Hawkins, J. E., 308.
 Hawkins, K., 218.
 Haworth, (Sir) N., 299,
 301.
 Haworth, R. D., 176, 182,
 189.
 Hawthorne, J. R., 281.
 Haynes, L. J., 133.
 Heap, R., 138.
 Hearn, P. F., 335.
 Heath, R. E., 116.
 Hecht, H., 85.
 Heer, J., 202, 205.
 Hegsted, D. M., 262.
 Heiber, W., 100.
 Heidelberger, M., 298, 299,
 301.
 Heilbron, (Sir) I., 130, 133,
 134, 206, 207, 208, 209,
 214, 216, 269, 277.
 Hein, F., 107.
 Heiple, H. R., 69.
 Heisig, G. B., 9, 22.
 Heiss, H., 189.
 Helland-Hansen, B., 338.
 Helz, A. W., 325.
 Hemingway, A., 243.
 Hempelmann, L. M., 252.
 Hems, B. A., 215.
 Henderson, J. E., 16.
 Henderson-Hamilton, J. C.,
 319.
 Hendry, J. A., 215.
 Henry, A. J., 332.
 Herbert, A., 196.
 Herczog, A., 91.
 Herd, R. L., 335.
 Herman, D. F., 96.
 Hermann, R., 328.
 Hérold, A., 86.
 Herrera, C. G., 87.
 Herrold, R. D., 304.
 Hertwig, K., 93.
 Herzfeld, K. F., 55.
 Herzog, J., 190.
 Hess, D. C., 115.
 Hess, K., 44, 45.
 Hess, T. M., 323.
 Hesse, B., 85.
 Hesse, E., 310.
 Hessling, H., 317.
 Heuser, G. F., 233.
 Hevesy, G., 84, 239.
 Hewett, L. F., 302.
 Hey, D. H., 51, 139, 157,
 159.
 Heyd, J. W., 159.
 Heyes, J., 326, 327.
 Heyworth, F., 130.
 Hickey, A., 219.
 Hilgermann, R., 310.
 Hill, D. W., 283.
 Hill, E. G., 274.
 Hill, M. A., 136.
 Hill, P., 180.
 Hillion, (Mlle.) P., 331.
 Hills, G. M., 309.
 Hincks, E. P., 116.
 Hinshaw, H. C., 293, 303,
 305, 306, 307, 308.
 Hinshelwood, (Sir) C., 51,
 52, 53, 54, 55, 57, 58, 60,
 67, 68, 69, 70, 71, 72, 73,
 74.
 Hipple, J. A., 14.
 Hirsch, A., 309.
 Hirschfelder, J. O., 10, 15,
 20, 22, 64.
 Hirst, E. L., 273, 281.
 Hitchcock, M. W. S., 277.
 Hitchings, G. H., 234.
 Hobbs, J. E., 59.
 Hobson, L. B., 308.
 Hobson, R. P., 173.
 Hodge, W. W., 215.
 Hodgson, H. H., 130,
 159.
 Höhn, R., 175, 177.
 Hofer, W., 205.
 Hoffhine, C. E., 308.
 Hofmann, A. W., 207.
 Hoggarth, E., 307, 309.
 Hohn, F., 213.
 Holmberg, B., 208, 209.
 Holmes, (Mrs.) B., 31.
 Holzapfel, L., 21, 23, 24.
 Honig, R. E., 6.
 Hood, R. L., 323.
 Hooper, I. R., 202.
 Hooykaas, R., 83.
 Hopher, T. H., 318.
 Hopkins, F. G., 245.
 Hopkins, S., jun., 176.
 Hopkins, S. H., 301.
 Hopwood, F. L., 8.
 Horn, D. H. S., 136.
 Horne, R. E., 271.
 Horning, E. C., 137.
 Horton, W. J., 211.
 Horton, W. S., 60.
 Horwitz, W., 114.
 Hosking, J. R., 180.
 Hotchkiss, R. D., 272, 275,
 281.
 Houben, J., 206, 208.
 Hough, L., 273, 281.
 Houlton, H. G., 341.
 Houtermans, F. G., 97.
 Houtmann, A. C., 236.
 Howard, G., 277.
 Howitt, F. O., 283.
 Howlett, K. E., 60.
 Howton, D. R., 156.
 Huang, H. T., 192.
 Hubbard, D. M., 325.
 Huber, W. F., 138.
 Huckaba, C. A., 104.
 Hudson, C. S., 203.
 Huebschmann, P., 294.
 Hürbin, M., 207.
 Hughes, E. W., 113.
 Hughes, G. K., 157.
 Hulburt, H. M., 60.
 Hulm, J. K., 90.
 Hultquist, M. E., 226, 227,
 233.
 Hulubei, H., 107.
 Hutchings, B. L., 226, 227,
 229, 230, 231, 233, 237.
 Hutchinson, C. A., 116.
 Hutchinson, G. W., 13.
 Hutchinson, W. S., 110.
 Hyde, E. K., 116.
 Hyman, H. T., 306.
 Ibanez, O. G., 343.
 Iland, C. N., 312.
 Ingeldt, G., 91.
 Ingersoll, A. W., 129.
 Ingold, C. K., 197.
 Ingold, W., 334.
 Ingram, G. L. Y., 302, 311.
 Ireton, H. J. C., 22.
 Irrmann, F., 89.
 Irvine, K. N., 300.
 Irving, H. M. N. H., 84.
 Isherwood, F. A., 271, 272,
 277.
 Ishiguro, T., 180.
 Ishmaui, Y., 310.
 Islay, O., 234.
 Israelashvili, S., 151.
 Ivancheva, A. G., 97.
 Ivancheva, E. G., 97.
 Ives, D. J. G., 107.
 Izzo, P. T., 131.
 Jablonowski, H., 101.
 Jackson, D. T., 332.
 Jacobi, E., 111.
 Jacobs, H., 185.
 Jacobs, M. B., 332, 341.
 Jacobsen, J. P., 338.
 Jacobson, R. D., 330.
 Jaffee, R. I., 98.
 Jahn, F. P., 57.
 Jahn, K. F., 104.

- Jakabeim, J. J., 101.
 James, D. G. L., 30.
 James, W. O., 274, 282.
 Jamieson, C. A., 278.
 Jamieson I. M., 343.
 Jansen, E. F., 201.
 Jansen, W. H., 326, 327.
 Jarrott, K. B., 158.
 Jazimirski, K., 336.
 Jean, M., 108, 109.
 Jefferies, H. S., 313.
 Jeffrey, G. A., 106.
 Jeffreys, H., 97.
 Jeger, O., 174, 176, 186, 204, 205.
 Jelley, J. W., 116.
 Jellinek, H. H. G., 60.
 Jenkins, 136.
 Jensen, E., 331.
 Jensen, E. U., 138, 140, 150, 152, 153.
 Jensen, H. F., 283, 286, 288.
 Jensen, K. A., 102, 111, 114.
 Jepson, J. B., 207.
 Jobling, J. W., 294.
 Jochimsen, E., 300.
 Johanny, S., 191.
 John, H. M., 262.
 Johnson, A. W., 132, 133, 158, 274, 282.
 Johnson, G. M., 331, 332.
 Johnson, H. O., 329.
 Johnson, J. R., 200.
 Johnson, M. J., 270, 277.
 Johnson, M. W., 338, 342.
 Johnson, R. S., 219.
 Johnson, T. B., 207, 215.
 Johnson, W. F., 42.
 Johnson, W. W. A., 325.
 Johnstin, R., 325.
 Johnston, H. L., 85.
 Johnston, T. Y., 194.
 Jolibois, P., 116.
 Jones, E. R. H., 133, 134.
 Jones, F. T., 90.
 Jones, G., 85.
 Jones, G. D., 217, 218.
 Jones, G. O., 86.
 Jones, J. K. N., 273, 281.
 Jones, R. G., 212.
 Jones, T. S. G., 275, 278, 280.
 Jones, W. E., 130.
 Jordan, C. W., 331.
 Jost, W., 67.
 Joyce, R. M., 151.
 Joyner, A. L., 298.
 Juda, W., 85.
 Juday, C., 342.
 Jukes, T. H., 227.
 Julian, P. L., 216.
 Jungers, J. C., 19, 22.
 Jungfleisch, (Mlle.) M. L., 90.
 Kabachnik, M. I., 138.
 Kaczka, E. A., 233.
 Kaertkemeyer, L., 21.
 Kagan, M. Y., 58.
 Kahn, E., 174.
 Kailan, A., 6, 22.
 Kaiser, H., 318, 322.
 Kalckar, H. M., 246.
 Kalle, K., 339, 340.
 Kamen, M. D., 239, 254, 260.
 Kampitsch, 84.
 Kantzer, (Mlle.) D., 101.
 Kapitanczyk, K., 94.
 Kaplan, N. O., 260, 261, 262.
 Kara-Michaelova, E., 16.
 Karabinos, J. V., 201, 204, 218.
 Karantassis, T., 114.
 Karimullah, 207.
 Karlson, A. G., 308.
 Karrer, P., 156, 201, 228, 234, 235, 236.
 Kasatotschkin, W., 104.
 Kasper, J. S., 92.
 Kassell, L. S., 56, 61, 67.
 Kassell, B., 286.
 Kassner, E. E., 331.
 Kassner, J. L., 331.
 Katzin, L. T., 116.
 Kaufmann, S., 177.
 Kauter, C., 174.
 Kay, H. F., 90.
 Kayne, G. G., 300.
 Kazeeva, E. V., 175.
 Keck, P. H., 322.
 Keck, R. H., 318.
 Keene, J. R., 14.
 Keesom, W. H., 82.
 Keighley, G., 276.
 Keimatsu, S., 180.
 Keiser, F. S., 77.
 Kelland, N. S., 77.
 Keller, R., 207.
 Kelly, W., 208.
 Kemmerer, G., 339, 340, 341.
 Kemp, J. W., 323.
 Kench, J. E., 254.
 Kennedy, C. R., 293, 300, 302, 306.
 Kennedy, D. J., 123.
 Kenner, G. W., 199, 214.
 Kenner, J., 196.
 Kenny, T. S., 215.
 Kent, P. W., 299, 301.
 Keresztesy, J. C., 199, 227, 231.
 Kern, W., 217.
 Kernbaum, M., 23.
 Kerr, W. A., 319.
 Kertscher, F., 327.
 Kessler, K. G., 323.
 Keston, A. S., 241, 276, 287.
 Ketchum, B. H., 340.
 Ketelaar, J. A. A., 99.
 Keuhemans, A. I. M., 134.
 Keyes, F. G., 104.
 Keys, A., 343.
 Kharasch, M. S., 118, 138, 140, 141, 146, 150, 152, 153, 154, 157, 160, 161.
 Kibler, R. F., 129.
 Kiers, R. J., 319.
 Kiessig, H., 44, 45, 47.
 Kindler, K., 206, 207, 211, 212.
 King, C., 319.
 King, E. J., 341.
 King, J. A., 211, 212, 213.
 King, W. H., 331.
 Kinley, W. N., 224.
 Kirby, H., 272.
 Kistiakowski, G. B., 64.
 Klebansky, A. L., 124.
 Kleiderer, E. C., 124.
 Klein, O., 12.
 Kleinberg, J., 86, 110, 111.
 Klem, A., 341.
 Klemm, L. H., 202.
 Klemperer, F. W., 251.
 Klevens, H. B., 38.
 Kline, G. M., 216.
 Kloetzel, M. C., 303, 310.
 Klute, C. H., 54, 60.
 Klyne, W., 328.
 Knight, B. C. J. G., 311.
 Knippenberg, E., 328.
 Knudsen, M., 338.
 Koch, H. P., 142, 161.
 Koch, J., 85.
 Koch, R., 299.
 Kocheshkov, K. A., 130.
 Koeck, H., 215.
 Körösy, F., 87.
 Kolb, J. J., 332.
 Kolmer, J. A., 305.
 Kolthoff, I. M., 42, 332, 336.
 Kolumban, A. D., 15.
 Komschilov, N. F., 175.
 Kondratev, V., 80.
 Kondratev, V. N., 75, 76, 79, 80.
 Kondrateva, E., 80.
 Kondrateva, E. I., 76, 79.
 Kondrateva, H., 76, 80.
 Kono, M., 175.
 Kopsch, U., 77.
 Kornberg, A., 265.
 Kornfield, E. C., 124.
 Kortüm, G., 110.
 Korzh, P. D., 325.
 Kosak, A. I., 129.
 Kosolapoff, G. M., 129, 138.
 Kossiakoff, A., 55.
 Kostyuchenko, L. A., 65.
 Kouba, D. L., 333.
 Kovalsky, A., 75.

- Krähenbuhl, W., 205.
 Kraft, K., 177.
 Krainich, H. G., 343.
 Kramer, W., 263.
 Kramers, H. A., 63.
 Krampitz, L. O., 261, 265.
 Krasny-Ergen, W., 116.
 Kraus, C. A., 38, 39.
 Krebs, H. A., 250, 265.
 Krenz, F. H., 18.
 Kreps, E., 340.
 Krestinski, V. N., 175.
 Krishnamurti, P., 45.
 Kriukov, P. A., 344.
 Krius, A., 106.
 Krogh, A., 341, 343.
 Kroll, W. J., 98.
 Kroner, T. D., 270.
 Krsek, G., 134.
 Kubaschewski, O., 104.
 Kuderna, B. M., 152.
 Kuehler, L., 60.
 Kuehl, F. A., 308.
 Kuehl, F. A., jun., 202.
 Kuh, E., 226, 227.
 Kulkarni, D. R., 107.
 Kummer, J. T., 100.
 Kuna, S., 308.
 Kunin, R., 116.
 Kuzin, A. M., 256.
 Kwantes, A., 134.
 Kwasnik, W., 100, 106, 109.
 Lachamp, F., 45.
 La Cour, L. F., 278.
 Lacourt, A., 215.
 Lafitte, M., 91.
 La Forge, F. B., 164, 165, 166, 167, 168, 169, 170, 171, 172, 173.
 Laidlaw, P. P., 298.
 Laitinen, H. A., 332.
 Lalande, W. A., jun., 177.
 Lambert, F. L., 160.
 La Mer, V. K., 331.
 Lampen, J. O., 205.
 Lamure, J., 91.
 Landler, I., 7.
 Landolt, F., 128.
 Lane, W. R., 334.
 Lange, B., 300.
 Lange, W., 102.
 Langmuir, I., 285.
 Langsjoen, A., 217.
 Langstroth, G. O., 319.
 Laning, S. H., 106.
 Laporte, R., 300.
 Larsen, A. H., 86.
 Larsh, A. E., 13.
 Larson, E. M., 82.
 Latarjet, R., 24.
 Latiu, E., 330.
 Laubengayer, A. W., 93.
 Leachlan, A. D. E., 333.
 Leatié, R., 107.
 Lautsch, W., 216.
 Lavin, G. I., 16, 25.
 Lawrence, A. S. C., 34, 57.
 Lawrie, R. A., 278.
 Lazarus, L. H., 37.
 Lea, D. E., 5, 6, 28, 31.
 Le Beau, L. S., 45.
 Lecante, J., 101.
 Lederer, M., 283.
 Lederer, N., 174.
 Lederle, P., 328.
 Lefort, M., 6, 23, 24.
 Lehmann, J., 306.
 Lehmann, W., 327.
 Leichter, 19.
 Leichtle, P. A., 320.
 Leifer, E., 54, 252.
 Leighton, P. A., 216.
 Leikend, M. C., 84.
 Lemaire, H. P., 88.
 Lemieux, R. V., 202.
 Leonard, J. W., 106.
 Le Peintre, M., 94.
 Lersson, E., 41.
 Lessing, F. P., 92.
 Lessmann, O., 94.
 Lesuk, A., 299.
 Letort, M., 52, 54.
 Letort, N. M., 54.
 Lettré, H., 192.
 Letts, E. A., 342.
 Leuchtenberger, C., 227.
 Leuchtenberger, R., 227.
 Leuckart, R., 129.
 Leutenegger, W. E., 156.
 Levene, P. A., 213.
 Levi, A. A., 268, 270, 272, 273, 275, 277, 282.
 Levi, M., 276, 287.
 Levi, T. G., 208, 213.
 Levin, R. H., 204.
 Levine, C., 274.
 Levine, H. A., 125.
 Levine, P., 283.
 Levine, R., 129.
 Levy, A. L., 216.
 Levy, E., 174.
 Levy, S., 317.
 Lew, B. W., 203.
 Lewis, B., 19, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77.
 Lewis, J. A., 84, 271.
 Lewis, M. R., 299.
 Lewisohn, R., 227.
 Li, T., 212.
 Libermann, D., 215.
 Lichtenberger, J., 136.
 Liddell, H. F., 276.
 Lieanu, C., 109.
 Lieb, H., 343.
 Liebhafsky, H. A., 86, 333.
 Liebig, G. F., 319.
 Liechti, A., 25.
 Lifson, N., 243, 263.
 Liggett, L. M., 113.
 Lilliendahl, W. C., 98.
 Lind, S. C., 6, 14, 18, 19, 21, 22.
 Lindenbaum, A., 254, 267.
 Lindley, H., 278.
 Lindner, F., 284.
 Lindsay, J. E., 333.
 Lindstrom, B., 275.
 Lingafelter, E. C., 38, 50.
 Lingane, J. J., 332, 333, 334, 337.
 Linggood, F. V., 282.
 Linhard, M., 101.
 Linkasiewicz, S. J., 136.
 Linstead, R. P., 84, 271, 283.
 Lipmann, F., 260, 261, 262.
 Lipton, M. A., 262.
 Littmann, E. R., 176.
 Litz, L. M., 116.
 Livingood, J. J., 288.
 Livingston, M. S., 10.
 Livingston, R., 9, 102, 116.
 Livingston, R. S., 18, 19, 21.
 Localio, S. A., 257.
 Lock, G., 136.
 Lockwood, W. W., 290.
 Loeb, L. B., 14.
 Loebel, R. O., 303.
 Loftfield, R. B., 95.
 Lohmann, A., 25.
 Loiseleur, J., 24, 30.
 Lomakin, B. A., 320.
 Lombard, R., 174, 176, 177, 183.
 London, I. M., 254, 259.
 Long, E. R., 292, 295, 298, 299, 303, 305, 310, 315.
 Long, S. H., 111.
 Longenecker, W. H., 272.
 Lopez, A. C., 312.
 Lorber, V., 243, 244, 263.
 Loscalzo, A. G., 334.
 Loudon, J. D., 193, 194, 195, 196, 198.
 Lounsbury, M., 85.
 Lourie, A., 319.
 Lowy, P. H., 276.
 Lucas, C. C., 341.
 Lucas, V. E., 159.
 Lucht, C. M., 92.
 Lütgert, I., 333.
 Lugg, J. W. H., 279, 282.
 Lukes, R., 176.
 Lundegårdh, H., 325, 327.
 Lunstman, B., 103.
 Lutz, A. H., 205.
 Lutz, F. B., 340.
 Lux, H., 111.
 Luyckx, A., 16.
 Lykken, L., 329.
 Lyman, J., 338.
 Lynen, F., 263.
 Lyness, W. I., 159.
 Lythgoe, B., 199, 205, 207, 209, 214.

- McBain, J. W., 37, 38, 39, 40, 41, 42, 50.
 McBay, H. C., 141, 146.
 McBride, J. J., 157.
 McCarter, J. R., 302, 311.
 McClosky, W. T., 305.
 McCollum, E. V., 279.
 McCombie, H., 138, 139.
 McCordock, H. A., 292.
 McCormack, W. B., 158.
 McCutcheon, P., 87.
 McDermot, W., 308.
 McDonald, D. K. C., 99.
 McDonald, R. A., 116.
 McElroy, O. E., 262.
 McEwen, W. L., 222, 223, 224.
 McFadyen, J. S., 214.
 McGilvery, R. W., 242.
 McHan, H., 41.
 McHargue, J. S., 330.
 Macheboeuf, M., 272.
 Machler, R. C., 319.
 McIlwain, H., 311, 312.
 McIntosh, A. V. jun., 204.
 McKail, J. E., 216.
 McKee, F. S., 77.
 McKenna, J. F., 217.
 Mackenzie, C. G., 252.
 MacKonzie, R. C., 74.
 McLennan, J. C., 22.
 McMillan, F. H., 211, 212.
 MacMillan, J., 193, 198.
 Macnamara, J., 92.
 McOmie, J. F. W., 208, 214.
 McPheat, J., 325.
 Macpherson, H. T., 287.
 McPherson, J. D., 175, 176, 177.
 McReynolds, R. C., 318.
 Macris, G. D'Costas, 332.
 McRoberts, T. S., 43.
 MacTurk, H. M., 311.
 McWhirter, M., 200.
 Maddock, A. G., 96, 116.
 Madigan, D. G., 306.
 Madinaveitia, J., 311.
 Madorsky, S. L., 91.
 Mäder, H., 317.
 Magat, M., 7.
 Magram, S. J., 59.
 Mahadevan, A. P., 130.
 Mahneke, H. E., 343.
 Majumdar, A. N., 113.
 Maki, T., 136.
 Malan, R. L., 212.
 Malaprade, L., 330.
 Malatesta, L., 113, 115.
 Malevskaja, S. S., 177.
 Maley, L., 84.
 Mallet, L., 16.
 Mallette, M. F., 233, 234.
 Malpica, J. T. M., 322.
 Malsch, J., 39.
 Mann, F. C., 293, 306, 307.
 Mann, F. G., 126, 138.
 Manolescu, T., 42.
 Manz, G., 198.
 March, L. E., 82.
 Marchand, B., 198.
 Marcovich, V. G., 79, 80.
 Margulis, H., 102.
 Marinsky, J. A., 83.
 Markarian, M., 157.
 Markham, R., 278.
 Marron, T. U., 42.
 Marshall, I., 158.
 Marshall, L. M., 277.
 Marshall, R. A., 277.
 Martin, A. J. P., 267, 268, 269, 270, 271, 272, 273, 274, 276, 277, 278, 279, 280, 282.
 Martin, A. R., 307, 309.
 Martin, D. R., 93.
 Martin, F. W., 22.
 Martin, G. J., 233.
 Martin, J. T., 165.
 Martin, L., 136.
 Maruyama, R., 175.
 Marvel, C. S., 154.
 Mas, R., 86.
 Mason, C. M., 94.
 Massey, H. S. W., 14.
 Massie, S. P., jun., 219.
 Masters, R. E., 254.
 Mathews, R. E. F., 278.
 Mathieson, A. McL., 105.
 Mathur, K. B. L., 155.
 Mattano, L. A., 212.
 Mattensen, L., 103.
 Matthews, D. J., 338, 340.
 Mattick, A. T. R., 309.
 Mattoon, R. W., 44, 47.
 Maw, G. A., 274, 282.
 Maximow, A. A., 295.
 Maxted, E. B., 82.
 May, A. N., 116.
 May, E. L., 214.
 Mayberry, M. G., 105.
 Mayer, R. L., 304.
 Mayer, S. W., 268.
 Mayors, K. R., 318.
 Médard, L., 104.
 Meerbott, W. K., 60.
 Megaw, (Miss) H. D., 90.
 Mehler, A. H., 265.
 Meikle, W. J., 333.
 Meinzer, E. M., 204.
 Meissner, G., 310.
 Melchior, J. B., 241.
 Melchior, N. C., 84.
 Mellanby, (Sir) E., 295.
 Mellon, M. G., 341.
 Mellor, D. P., 84, 95, 114.
 Melliush, R. R., 133.
 Meloche, V. W., 339, 340.
 Melville, D. B., 199.
 Melville, K. I., 310.
 Melvin, E. H., 325.
 Mendelssohn, K., 85.
 Menzel, A. E. O., 301.
 Mercer, R. D., 233.
 Meredith, W. J., 25.
 Merrill, R. C., 42.
 Merritt, R. P., 163.
 Merz, J. H., 159.
 Metayer, M., 124.
 Metchnikoff, 293.
 Metzler, D. E., 332.
 Meulen, P. A. van der, 106.
 Meyer, G. M., 213.
 Meyer, K., 191.
 Meyer, K. H., 46.
 Meystre, C., 156.
 Micheel, F., 213.
 Michel, (Mme.) A., 112.
 Michelson, A. M., 138.
 Middlebrook, W. R., 274.
 Miescher, K., 156, 202, 205.
 Mikkelsen, D. S., 329.
 Milas, N. A., 59, 146.
 Miles, A. A., 301.
 Miller, G. L., 284, 286.
 Miller, N., 8, 9, 31, 32.
 Miller, W. W., 95.
 Millington, R. H., 263.
 Mills, H., 105.
 Minder, W., 25.
 Minkoff, G. J., 77, 104, 149.
 Misra, G. S., 157.
 Mitchell, A. D., 82.
 Mitchell, H. K., 226.
 Mitchell, R. L., 324, 329.
 Mittelmann, R., 280.
 Mitton, H. E., 110.
 Miyamichi, E., 207.
 Mizel, A. E. O., 299.
 Moeller, T., 94, 100, 116.
 Moen, J. K., 299.
 Mohler, F. L., 13.
 Montavon, R. M., 204.
 Montignie, E., 93, 99, 107.
 Moon, C. H., 19.
 Moore, B. P., 182, 189.
 Moore, C. V., 254.
 Moore, M. L., 129.
 Moore, S., 271, 272, 279.
 Moore, T. E., 102.
 Morette, A., 103.
 Morgan, W. T. J., 274, 281.
 Morgana, M., 176.
 Moring-Claesson, I., 243.
 Moritz, H., 318, 319, 320.
 Morris, J. C., 53.
 Morrison, G. A., 280.
 Morse, S., 10, 24.
 Moses, H. E., 305.
 Mosley, V. M., 275, 280.
 Moss, J., 233.
 Moss, M. L., 376.
 Motschan, I., 6.
 Mowat, J. H., 226, 227, 230, 231, 233, 237.
 Mowry, D. T., 126, 127.
 Moyer, A. W., 221.

- Moyle, V., 271, 277.
 Mozingo, R., 124, 199, 200, 223, 233.
 Müffling, L. von, 81.
 Mueller, D. W., 14.
 Müller, R. H., 326.
 Muir, E., 306.
 Muir, H. M., 255.
 Mukerjee, S., 203.
 Mullinger, L. W., 116.
 Mund, W., 6, 18, 19, 21, 22.
 Munday, B., 299.
 Mundell, M., 277.
 Munter, P. A., 278.
 Muntwyler, O., 172.
 Murgulescu, I. G., 330.
 Murray, A. G., 215.
 Murray, E. H., 136.
 Murray, W. M., 320.
 Muschenheim, C., 308.
 Mushett, C. W., 308.
 Mustafa, A., 135.
 Mutter, W. E., 58.
 Myei, N., 304.
 Myers, A. J., 325.
 Myers, A. T., 329.
 Myers, R. J., 332.
 Myers, W. R., 111.
 Nachmansohn, D., 262.
 Nachod, F. C., 333.
 Nadeau, G. F., 336.
 Nahstoll, G. A., 323.
 Naik, K. G., 100.
 Nalbandy, A. B., 69, 71, 75, 77.
 Nast, R., 100.
 Nayar, M. R., 111.
 Naylor, J., 341.
 Nazzewski, M., 157.
 Nègre, L., 301.
 Neher, R., 156.
 Nehring, K., 328.
 Neu, R., 165.
 Neubauer, L. G., 180, 182.
 Neuberger, A., 255, 291.
 Neudorffer, J., 109.
 Neufeld, O. E., 335.
 Neuhaus, C. J., 320.
 Neumann, M. M. C., 217.
 Newbold, G. T., 214.
 Newbound, K. B., 319.
 Newman, M. S., 128, 302, 311.
 Nichols, J., 215.
 Nichols, M. L., 325.
 Nicholson, J. S., 189.
 Niederhauser, W. D., 125.
 Nielsen, J. K., 308.
 Nielsen, K., 89.
 Niemann, C., 334, 337.
 Nier, A. O., 85, 243.
 Nierenstein, M., 189.
 Nigre, L., 310.
 Nilssen, B., 331.
 Nishigaki, M., 310.
 Nishina, Y., 12.
 Nisoli, C., 205.
 Nocito, V., 244.
 Noonan, T. R., 254.
 Nordblom, G. F., 101.
 Norman, D. P., 325.
 Norris, L. C., 233.
 Norris, L. D., 95.
 Norris, T. H., 95.
 Norrish, R. G. W., 77.
 Northey, E. H., 226, 227.
 Norymberska, L., 202.
 Norymberski, J., 202, 204, 205.
 Nosenko, D. S., 65.
 Novak, A., 175.
 Novelli, G. D., 262.
 Nozaki, K., 143, 145, 147.
 Nurnberger, C. E., 24.
 Nyholm, R. S., 112, 113, 115.
 Nystrom, R. F., 122, 123.
 Oberhauser, F., 106.
 O'Brien, T. D., 92, 107.
 Ochoa, S., 265, 266.
 O'Connor, J. J., 40.
 O'Connor, R. T., 325.
 O'Dell, B. L., 229.
 Örstrom, A., 250.
 Örstrom, M., 250.
 Oesper, R. E., 333.
 Ogg, E. F., 21.
 Ogg, R. A., 56.
 Ogg, R. A., jun., 99, 100.
 Ogblethorp, G. C., 332.
 Ogston, A. G., 284.
 Ohe, H., 123.
 Ohle, H., 218.
 Ohlendorf, H., 130.
 Olalde, A., 202.
 Olcott, H. S., 291.
 Oldenburg, O., 16, 69, 76.
 Oldfield, J. H., 326.
 Oleson, J. J., 233.
 Ollis, W. D., 214.
 Olmer, L. J., 106.
 Olsen, N. S., 243, 244.
 Openshaw, H. T., 138, 208.
 Opie, E. L., 294.
 Oppenheim, J. C., 335.
 Oppenheimer, E. H., 294.
 Oppenheimer, H., 40, 41.
 Oriana, R. A., 109.
 Ormont, B., 87.
 Ormondt, J. van, 88.
 O'Rourke, L., 312.
 Orten, J. M., 277.
 Osadchih, M., 340.
 Osipov, V. N., 102.
 Ostertag, (Mlle.) H., 89.
 Oswald, E. J., 308.
 Ott, A. C., 212.
 Overell, B. T., 282.
 Overman, R. R., 329.
 Owen, L. N., 123.
 Owsley, W. D., 318.
 Oxford, A. E., 142.
 Oxley, M. W., 127, 128.
 Oza, T. M., 100.
 Pacilli, (Signa.) E., 86.
 Page, E., 279.
 Page, J. E., 132.
 Pagel, W., 300.
 Paige, M. F. C., 309.
 Paine, F. J., 309.
 Palin, D. E., 95.
 Palit, S. R., 335.
 Palkin, S., 174, 176, 177, 178, 179.
 Pamfilov, A. V., 97.
 Paneth, F. A., 85.
 Panizzon, L., 214.
 Papa, D., 201, 212.
 Paquette, R. G., 38.
 Paris, R., 101.
 Park, G. S., 159.
 Parker, L. F. J., 278.
 Parkes, T. D., 329.
 Parks, R. Q., 324.
 Parry, R. W., 107.
 Parsons, D. S., 280.
 Parsons, J. L., 332.
 Parsons, L. B., 105.
 Partington, R. G., 60.
 Partridge, M. W., 127, 278.
 Partridge, S. M., 274, 281, 283.
 Pascal, P., 107.
 Pasternak, V. Z., 182.
 Patat, F., 52.
 Patel, S. Z., 100.
 Patrick, W. L., 22.
 Patry, M., 99.
 Patterson, W. I., 277.
 Pattison, D. B., 211.
 Patton, A. R., 274.
 Paul, A. J., 305.
 Pauling, L., 82, 84.
 Pauly, A., 301.
 Pauson, P. L., 189.
 Pavlov, D. S., 79.
 Pavlov, V. I., 7.
 Peacock, M. A., 89.
 Peak, D. A., 207, 210.
 Pearson, W. H., 96.
 Pearson, T. G., 16, 105.
 Pease, R. N., 51, 52, 55, 57, 59, 65, 68, 69.
 Peck, R. L., 297, 308.
 Pecsok, R. L., 333.
 Pelzer, H., 62, 63.
 Pekarek, E., 290.
 Penner, M., 306.
 Percival, E. G. V., 281.
 Pereira, G. J., 343.
 Perkin, A. G., 189, 190.
 Perkins, F. M., 190.
 Perkins, P. D., 136.
 Perkins, W. A., 216.
 Perouze, J., 106.

- Perrin, M. W., 22.
 Perry, J. M., 22.
 Persson, S. H., 110.
 Peschke, W., 206.
 Petering, H. G., 235.
 Peters, E. D., 335.
 Petersen, M. H., 270.
 Petersen, W., 294.
 Peterson, B. W., 25.
 Peterson, E. W., 323.
 Peterson, W. H., 226, 277, 342.
 Petrich, K., 332.
 Petrov, A. A., 126.
 Peyronel, G., 86.
 Pfau, G. M., 215.
 Pfeiffer, M., 170.
 Pfeilsticker, K., 322, 325.
 Pfaffner, J. J., 229.
 Pfister, R. J., 323.
 Pfuetez, K. H., 306.
 Philippoff, W., 44, 45, 47.
 Phillips, D. M. P., 273, 274, 278, 289.
 Phillips, H., 274, 276.
 Phillips, J. T., 8.
 Phillips, M. A., 130.
 Philippon, A. T., 277.
 Pickel, F. D., 214.
 Pierron, P., 110.
 Pierson, E., 131.
 Pietrusza, E. W., 153.
 Piffault, 24.
 Piggot, H. A., 197.
 Piggott, W. A., 127.
 Pillemer, L., 301.
 Pinazzi, C., 105.
 Pink, R. C., 43.
 Pinkston, J. T., jun., 109.
 Pinner, M., 299.
 Pitter, A. V., 37.
 Pittman, R. W., 107.
 Platz, H., 79.
 Plentl, A. A., 246.
 Plimmer, H., 180.
 Poe, C. F., 260.
 Poetzelberger, R., 317, 319.
 Pohl, W., 173.
 Polanyi, M., 69.
 Polgar, N., 297, 298, 314.
 Polglase, W. J., 202, 215.
 Pollard, A. J., 271.
 Pollock, M. W., 128.
 Polly, O. L., 52.
 Polonovski, M., 215.
 Polson, A., 275, 278, 280.
 Polyakov, M. V., 65.
 Popescu, M., 43.
 Popov, L. D., 124.
 Popper, P., 90.
 Portal, E., 87.
 Porter, F., 21.
 Porter, R. R., 277.
 Portevin, A., 86.
 Postovskii, I. Y., 310.
 Potter, C., 165.
 Potts, G. D., 99.
 Potts, J. E., jun., 99.
 Pouget, L., 340.
 Pound, J. R., 332.
 Pourbaix, M., 90, 104.
 Powell, C. F., 5.
 Power, F. B., 314.
 Pozhiltzova, E. A., 128.
 Praagh, G. van, 96.
 Pramanik, B. N., 313.
 Pratt, J. J., 274.
 Prelog, V., 204, 205.
 Prettre, M., 69.
 Price, C. C., 139, 157.
 Price, D., 214.
 Price, T. D., 95.
 Priest, H. F., 108.
 Priejs, B., 205, 307.
 Prill, E. J., 154.
 Prince, A. L., 329.
 Prins, D. A., 203.
 Prins, H. J., 96.
 Probst, R. E., 85.
 Prokof'ev, V. K., 317.
 Prytherch, H. F., 344.
 Pugh, W., 332.
 Pupko, S., 99.
 Purkayastha, B. C., 98.
 Pushkareva, Z. V., 310.
 Quaglini, J. V., 77.
 Quarrell, A. G., 317.
 Quast, G., 310.
 Querry, M. V., 221, 222, 223.
 Quilliam, J. P., 139.
 Quilliam, T. A., 139.
 Quinby, O. T., 101.
 Quintin, (Mlle.) M., 91.
 Raab, W., 310, 313.
 Raben, E., 338, 340, 342.
 Rabinowitch, E., 17.
 Radin, N. S., 239.
 Raffel, S., 300.
 Rai, J., 155.
 Raistrick, B., 188.
 Rajchman, J. A., 323.
 Rake, G., 308, 309.
 Rakestraw, N. W., 340, 343.
 Raleigh, G. W., 307.
 Raley, J. H., 59, 146, 147, 149.
 Ralph, C. C., 320.
 Ralston, A. W., 37, 38, 39.
 Ramachandran, B. V., 106.
 Ramage, H., 325.
 Ramberg, L., 331.
 Ramsay, (Sir) W., 7.
 Ramsey, L. L., 277.
 Ramsperger, H. C., 55, 61.
 Ramstetter, H., 65.
 Randall, S. S., 272.
 Rank, D. H., 323.
 Raper, R., 273.
 Rathje, W., 327.
 Ratner, S., 241, 244.
 Rau, M. G., 163.
 Raudnitz, H., 174.
 Rauteberg, E., 328.
 Ravel, J. M., 233, 250.
 Ray, P., 113.
 Ray, R. C., 88, 111.
 Raymond, S., 87.
 Raynaud, A., 86.
 Razumova, S. A., 114.
 Rea, F. W., 342.
 Read, J., 6.
 Reber, F., 214.
 Rebstock, M. C., 308.
 Redfield, A. C., 340.
 Reed, H. W. B., 169, 173.
 Rees, M. W., 287.
 Reichard, P., 246, 282.
 Reichstein, T., 191, 203, 214.
 Reid, E. E., 334.
 Reid, J. C., 212.
 Reid, W. B., jun., 201.
 Reiling, V. E., 16.
 Reinhold, H., 105.
 Reigner, G., 318.
 Reinmuth, O., 152.
 Reis, L., 243.
 Reitz, H. C., 291.
 Renfrew, 298.
 Reno, N. E., 137.
 Renquist, M. L., 216.
 Rentschler, H. C., 98.
 Reppe, J. W., 132.
 Rhoads, C. P., 257.
 Rhodes, R. G., 90.
 Riabtschikov, D. I., 115.
 Riblett, E. W., 57.
 Ricci, J. E., 52.
 Rice, F. O., 52, 54, 55, 60.
 Rice, O. K., 56, 61.
 Rich, A. R., 292, 293, 297, 299, 300.
 Richardson, D., 328.
 Richardson, E. M., 214.
 Richardson, G. M., 336.
 Richardson, H. B., 303.
 Richmond, J. H., 195.
 Richter, C., 326, 327.
 Rickes, E. L., 231.
 Riddel, W. A., 342.
 Rideal, E. K., 18.
 Rider, A. A., 279.
 Riehm, H., 328.
 Rieke, F. F., 76.
 Rienäcker, G., 106.
 Riener, T. W., 124, 125.
 Riggert, K., 5.
 Riley, D. P., 48.
 Riley, G. A., 344.
 Rimington, C., 257, 259, 273.
 Ripan, R., 109.
 Ripert, J., 165.
 Risler, T., 96.
 Risse, O., 23, 24, 25.

- Rist, N., 305.
 Ritchie, M., 51, 74.
 Rittenberg, D., 212, 239,
 241, 242, 246, 249, 252,
 253, 254, 255, 259, 262.
 Rivenq, F., 103.
 Rivers, R. V. P., 214.
 Roberts, J. S., 61.
 Robertson, A., 155, 159.
 Robertson, J. M., 105.
 Robertson, N. C., 65.
 Robinson, C., 39.
 Robinson, H. A., 334.
 Robinson, P. L., 92, 105.
 Robinson, (Sir) R., 131,
 200, 207, 208, 297, 298,
 300, 314.
 Robinson, R. A., 112.
 Robinson, R. I., 339, 340.
 Robinson, R. J., 339, 341,
 342, 343.
 Roblin, R. O., jun., 205.
 Rochford, D., 342.
 Rochow, E. G., 97.
 Rodden, C. J., 286.
 Rodebush, W. H., 77.
 Rodriguez, M. M., 104.
 Roe, E. M. F., 192, 194.
 Roe, J. W., 42.
 Roelen, O., 134.
 Rogers, L. H., 324, 325.
 Roginsky, S., 6.
 Rogler, E., 85.
 Rohmleher, L., 327.
 Rohner, F., 317, 318.
 Rohrback, G. H., 109.
 Roll, P. M., 246, 250, 251.
 Rollefson, G. K., 54, 95.
 Rollinson, C. L., 82.
 Rose, F. L., 215.
 Rose, J. D., 176.
 Rosenberg, I. M., 267.
 Rosenblum, C., 21, 23.
 Rosenheim, O., 273.
 Rosetti, F., 10.
 Ross, A. G., 281.
 Ross, D. J., 182.
 Ross, S. D., 157.
 Rossiiskaya, P. A., 138.
 Roth, L. J., 252.
 Roth, W. L., 54.
 Rothen, A., 289.
 Roudier, A., 281.
 Rougeot, L., 99, 106.
 Rowley, H. H., 60.
 Rubin, L. C., 57.
 Rubinstein, A. M., 114.
 Rudall, K. M., 286.
 Rue, S. O., 331.
 Rüdorff, G., 95.
 Rüdorff, W., 95, 96.
 Ruehle, A. E., 317, 324, 334.
 Ruhemann, S., 219.
 Rule, A. M., 305.
 Rumpf-Nordmann, (Mme.)
 M. E., 104.
 Rundle, R. E., 116.
 Runnicles, D. F., 42.
 Rushbrooke, G. S., 61.
 Rushman, D. F., 90.
 Russell, H., 82.
 Russell, R. G., 325.
 Rust, P. F., 59, 146, 147,
 148, 149.
 Rutan, P. V., 211.
 Ruzicka, L., 119, 162, 163,
 164, 165, 166, 168, 170,
 171, 172, 173, 174, 176,
 177, 178, 184, 185, 186,
 205, 207.
 Ryder, C. T., 297.
 Rydon, H. N., 276, 277.
 Ryman, B. E., 215.
 Rymer, J., 309.
 Rys, I. G., 93.
 Sabin, F. R., 292, 295, 297,
 298.
 Sachsse, H., 52.
 Sacks, J., 35, 239, 314.
 Safir, S. R., 221, 222, 223.
 Sahai, R. B. N., 111.
 Sahney, R. C., 111.
 Sahyun, M., 288.
 Sakami, W., 243, 244, 263.
 Sakellarides, P., 114.
 Sakurada, Y., 208.
 Salomon, K., 254.
 Saluste, E., 243.
 Samak, B., 332.
 Samis, C. S., 39.
 Sanderman, W., 175, 176,
 177.
 Sanderson, T. F., 174, 175,
 179, 180.
 Sandin, R. B., 158.
 Sanger, F., 277, 279, 288, 289.
 Santavý, F., 192.
 Sauer, H., 96.
 Saunders, B. C., 126, 138,
 139.
 Saunders, J. A., 333.
 Saunders, K. H., 158.
 Sauderson, J. L., 319, 322,
 323.
 Sawyer, R. A., 317, 319.
 Scarisbrick, R., 271, 277.
 Schaeppi, Y., 107.
 Schafer, K., 85.
 Schatz, A., 307.
 Schaufelberger, F., 91.
 Schechter, A., 6.
 Schechter, W. H., 86.
 Schenk, P. W., 79, 80, 101,
 106.
 Scheuer, O., 23.
 Schifferli, J., 42.
 Schifflett, C. H., 22.
 Schilling, J. R., 279.
 Schlechten, A. W., 98.
 Schlesinger, H. I., 122.
 Schmeidler, G. A., 183.
 Schmeisser, M., 100, 101.
 Schmid, H., 156, 201.
 Schmitt, L., 327.
 Schmitz, H., 109.
 Schmitz-Dumont, O., 102.
 Schneider, E., 105.
 Schneider, E. G., 76.
 Schnider, O., 200.
 Schnizlein, J. G., 94.
 Schönberg, A., 135.
 Schoenheimer, R., 239, 241,
 245, 246.
 Schöning, I., 41.
 Schoental, R., 198.
 Schoepfle, C. S., 22.
 Schomaker, V., 105.
 Schramm, R., 137.
 Schröer, E., 333.
 Schubert, C. C., 60.
 Schubert, J., 254, 267.
 Schubert, J. D., 267.
 Schuch, J., 319.
 Schuch, J. A., 326.
 Schuhknecht, W., 327.
 Schulman, J. H., 43, 48.
 Schulman, M. P., 242.
 Schultze, A., 132.
 Schultze, G. R., 60.
 Schumacher, H. J., 51, 59,
 109.
 Schumb, W. C., 97, 108.
 Schwabacher, H., 304.
 Schwarz, R., 96, 97, 100.
 Schwarz, W., 326.
 Schwarzenbach, G., 84, 187.
 Schweitzer, G. K., 116.
 Schwenk, E., 201, 212.
 Schwob, Y., 89.
 Schwyzer, R., 228, 235,
 236.
 Scott, A. B., 38, 50.
 Scott, D. A., 288, 290, 291.
 Scott, G. P., 192.
 Scott, (Miss) J. D., 82.
 Scott, M., 309.
 Scott, M. L., 233.
 Scott, R. O., 321, 324.
 Scott, T. R., 93, 98.
 Scribner, B. F., 318.
 Seaborg, G. T., 116, 117.
 Sealock, R. R., 285.
 Sears, C. A., 136.
 Sease, J. W., 337.
 Sedov, J. S., 318.
 Seeger, D. R., 226, 227, 233.
 Seel, F., 102.
 Segel, E., 137.
 Seibert, F. B., 298, 299, 301,
 303.
 Seibt, S., 172.
 Seith, W., 317.
 Sellers, H. G., 144.
 Selwood, P. W., 94.
 Selye, H., 302.
 Semb, J., 226, 227, 230, 231,
 233, 237.

- Semenov, N. N., 67, 69, 75,
 77, 78, 79, 81.
 Semon, W. F., 158.
 Sengir, E., 310.
 Sen-Sarma, R. N., 98.
 Serijan, K. T., 218.
 Seubold, F. H., 59, 147,
 148, 149.
 Sexton, W. A., 92.
 Shaffer, P. A., 334.
 Shah, C. C., 100.
 Shanley, E. S., 104.
 Shantarovich, P., 77.
 Shantz, E. M., 212.
 Shaw, G., 208.
 Shaw, G. T., 59.
 Shaw, J., 273.
 Shaw, J. A., 88.
 Shaw, J. H., 100.
 Sheehan, J. C., 131.
 Sheets, D. G., 206.
 Shemin, D., 239, 241, 242,
 249, 253, 254, 255, 259.
 Sheppard, C. W., 6.
 Sherman, H., 299.
 Sherrard, E. C., 189.
 Sherry, P. G., 219.
 Sherwood, I. R., 180.
 Sheverdina, N. I., 130.
 Shipley, F. W., 201.
 Shishakov, N. A., 24.
 Shive, W., 233, 250.
 Shockley, W., 86.
 Shoppee, C. W., 155, 197.
 Shorr, E., 303.
 Short, W. F., 127, 128, 180.
 Shovers, J., 333.
 Shrader, E. F., 110.
 Shubina, S., 69, 77.
 Shulek, E., 333.
 Sickels, J. P., 226, 227.
 Sickman, D. V., 52.
 Siebert, H., 94.
 Siedel, W., 259.
 Siegwart, J., 208, 235.
 Siffert, R. H., 285.
 Siggia, S., 334.
 Silber, P., 89.
 Silbiger, G., 92.
 Silbur, R. H., 308.
 Sillén, L. G., 91, 103, 268.
 Silver, S. D., 337.
 Silverstein, M. S., 101.
 Simon, E., 40.
 Simon, F. E., 86.
 Simonenko, D. L., 98.
 Simons, J. H., 96.
 Simonsen, (Sir) J., 163.
 Simpson, J. E. C., 229.
 Sinclair, D. A., 819.
 Sinex, M., 267.
 Singh, S., 111.
 Sinha, P. C., 88.
 Sisler, H. H., 86, 97.
 Sjögren, B., 284.
 Skell, P. S., 153.
 Skolnik, S., 101.
 Skorodumov, V. A., 218.
 Slack, C. M., 7.
 Slack, R., 159.
 Slater, N. B., 62, 63.
 Slimowicz, C. E., 182.
 Sloane, N. H., 229.
 Slotin, L., 252.
 Slotkin, G. E., 314.
 Slottman, G. V., 41.
 Smith, A. H., 277.
 Smith, C., 15.
 Smith, C. G., 332.
 Smith, D. M., 316.
 Smith, E. C. B., 274, 282.
 Smith, E. L., 132, 275, 278,
 282.
 Smith, G. F., 331, 332.
 Smith, G. S., 317.
 Smith, H. M., 86.
 Smith, H. P., 25, 340.
 Smith, J. H., 55, 56.
 Smith, J. M., jun., 226, 227,
 233.
 Smith, T. R. E., 52, 53, 54, 58.
 Smith, K. M., 278.
 Smith, L. I., 215.
 Smith, M. I., 306.
 Smith, M. J., 305.
 Smith, N., 333.
 Smith, N. O., 107.
 Smith, R. E., 52.
 Smith, S., 305.
 Smith, W. T., jun., 111.
 Smith, W. V., 69, 76.
 Smithburn, K. C., 297, 298.
 Smyth, C. P., 109.
 Smyth, H. D., 14.
 Snell, A. H., 95.
 Snell, E. E., 226.
 Snow, G. A., 311.
 Snyder, H. R., 157.
 Snyder, R. L., 323.
 Sober, H. A., 337.
 Sørensen, N. A., 180.
 Soldate, A. M., 42.
 Soll, J., 106.
 Solomon, A. K., 241.
 Solotorovsky, M., 308.
 Soloway, S. B., 168, 169,
 173.
 Sommer, F., 333.
 Sommer, L. H., 153, 156.
 Sommers, A. H., 218.
 Sommers, H. S., 69, 76.
 Somogyi, Z., 336.
 Sonderhoff, R., 263.
 Sondheimer, F., 133.
 Sonne, J. C., 247.
 Soper, Q. F., 212.
 Soper, W. B., 293.
 Sopor, N. P., 120.
 Sorkin, E., 205.
 Sorkin, M., 191.
 Soskin, S., 283.
 Souhay, P., 103, 108, 109.
 Southwick, P. L., 233.
 Spark, A. H., 275, 282.
 Sparks, J., 174.
 Spatz, S. M., 219.
 Speakman, J. B., 157.
 Speakman, J. C., 333.
 Speck, J. F., 266.
 Spencer, C., 124, 199.
 Sperber, E., 243.
 Spero, G. B., 204.
 Spielman, M. A., 211.
 Splitter, J. S., 129.
 Spoor, H. J., 341.
 Spring, F. S., 122, 124, 214.
 Sprinson, D. B., 244, 250.
 Sproul, E. E., 242.
 Srivastava, L. N., 111.
 Stabel, W., 13.
 Stace, H. C. T., 329.
 Stacey, G. J., 138.
 Stacey, M., 299, 301.
 Stadler, H. P., 106.
 Stadtman, E. R., 260.
 Stamm, H., 105, 106.
 Stanck, J., 211.
 Stanley, W. M., 35, 314.
 Starr, D. D., 116.
 Staudinger, H., 119, 162,
 163, 164, 165, 166, 168,
 170, 171, 172, 173, 208.
 Stauff, J., 44, 45, 46.
 Staveley, L. A. K., 52, 58.
 Steacie, E. W. R., 19, 51,
 53, 58, 59, 60, 139.
 Stearns, R. S., 40, 47.
 Steger, L., 214.
 Stehle, R. L., 310.
 Stein, G., 30, 159.
 Stein, W. H., 271, 272, 279.
 Steinbach, M. M., 310.
 Steinbuch, W., 234.
 Steiner, R., 84.
 Stenström, W., 10, 25.
 Stephen, J. M. L., 278, 289.
 Stephenson, D., 305.
 Stephenson, M., 265.
 Stepka, W., 272, 276, 278.
 Stepukhovich, A. D., 60.
 Stern, K. G., 290.
 Sternbach, L., 174, 176,
 177, 178.
 Stetten, M. R., 250.
 Stevens, A. B., 189.
 Stevens, A. J., 97.
 Stevens, P. G., 195.
 Stevens, T. S., 214.
 Stevenson, J. K., 159.
 Steward, F. C., 272, 278,
 325.
 Stewart, F. B., 16, 25.
 Stewart, K., 99.
 Stewart, R., 125.
 Stjärnholm, R., 243.
 Stock, J. T., 333, 334.
 Stoddart, E. M., 54.
 Stodola, F. N., 299.

- Stokes, J. L., 231.
 Stokland, K., 96.
 Stokstad, E. L. R., 226,
 227, 229, 230, 231, 233,
 237.
 Stone, H. W., 333.
 Story, R. V., 321.
 Stott, V., 334.
 Strachan, S. J., 306.
 Strafford, N., 325.
 Strain, W. H., 257.
 Strecker, H., 261.
 Street, H. R., 10.
 Strivens, M. A., 90.
 Strock, L. W., 321, 324.
 Studier, M. H., 116.
 Sturgis, B. M., 216.
 SubbaRow, Y., 222, 223,
 226, 227, 229, 230, 231,
 233, 237.
 Suckfäll, 213.
 Süe, P., 84.
 Suess, H. E., 83.
 Sullivan, W. N., 173.
 Sully, B. D., 332.
 Sulman, F., 302.
 Surgenor, D. M., 59, 146.
 Suter, C. M., 137.
 Suter, E., 307.
 Suter, H. S., 85.
 Sutherland, G. B. B. M.,
 100, 276, 287.
 Svedberg, T., 284.
 Sverdrup, H. U., 338.
 Swank, H. W., 341.
 Swann, S., jun., 107.
 Swanton, A., 189.
 Sweeney, T. R., 198.
 Swern, D., 135.
 Swift, E. H., 332, 337.
 Swift, H. F., 299.
 Swift, P. N., 306.
 Sykes, P., 208.
 Sylvester, R. F., jun., 233.
 Synge, R. L. M., 267, 268,
 269, 270, 271, 273, 274,
 276, 279.
 Szebellédy, L., 336.
 Szegehő, F., 333.
 Szpilfogel, S., 205.
 Szwarc, M., 60, 61.
 Ta, Y., 83.
 Takvorian, S., 115.
 Tallichet, A., 186.
 Tamarelli, R. M., 268.
 Tanford, C., 59.
 Tarbell, D. S., 192, 194,
 198.
 Tarbutton, G., 101.
 Tardy, P., 101.
 Tartar, H. V., 38, 50.
 Tarver, H., 241.
 Tattersfield, F., 173.
 Tatch, E. J., 106.
 Taurinā, A., 196.
 Taylor, A. H., 52.
 Taylor, E. C., jun., 233,
 234.
 Taylor, H. A., 57, 59.
 Taylor, H. S., 20, 22.
 Taylor, J. K., 334.
 Taylor, L. S., 13.
 Taylor, M. C., 332.
 Taylor, M. D., 98.
 Tchakirian, A., 97, 109.
 Teller, E., 55.
 Teorell, T., 341.
 Terem, H. N., 89.
 Terentiev, A. P., 126.
 Terentieva, E. A., 115.
 Terjessen, S. G., 270.
 Tesar, C., 246.
 Tesluk, H., 279.
 Thamer, R., 102.
 Thanheiser, G., 326.
 Thelin, J. H., 106.
 Theobald, H., 23.
 Theodorof, P., 6.
 Thode, H. G., 85, 92.
 Tholin, G., 113.
 Thomas, C. C., 292.
 Thomas, E. W. P., 313.
 Thomas, H., 263.
 Thomas, H. C., 268.
 Thomas, L. F., 116.
 Thomas, R. M., 297, 300.
 Thompson, D. L., 302.
 Thompson, H. L., 302.
 Thompson, H. W., 77, 136.
 Thompson, J. P., 272.
 Thompson, R. B., 159.
 Thompson, R. M., 89.
 Thompson, R. O., 314.
 Thompson, T. G., 338, 339,
 341, 342, 343.
 Thorndike, E. M., 319.
 Thruston, M. N., 325.
 Tickner, A. W., 95.
 Tiggelen, A. van, 21.
 Tinker, J. F., 205, 250.
 Tischer, J., 339.
 Tiselius, A., 269, 270.
 Tishler, M., 131, 236.
 Tiskhoff, G. H., 279.
 Titus, L., 339, 340.
 Todd, A. R., 138, 199, 203,
 205, 207, 208, 209, 214.
 Todd, D., 181.
 Toennies, G., 274.
 Tolman, L., 233.
 Tomkief, S. I., 116.
 Tomlinson, A. J. H., 42.
 Tomlinson, H. M., 331.
 Tompkins, E. R., 268.
 Tompkins, F. C., 88.
 Tompsett, R., 308.
 Topham, A., 208.
 Toscani, V., 329.
 Toth, S. J., 329.
 Tracey, A., 325.
 Traube, J., 41.
 Traube, W., 130, 215.
 Trautner, E. M., 335.
 Treadwell, W. D., 89, 91,
 107, 319.
 Trenner, N. R., 231.
 Tresadern, F. H., 173.
 Tribalat, (Mlle.) S., 111.
 Tristram, G. R., 271, 276,
 287.
 Troitzkaja, A. D., 114.
 Truog, R., 329.
 Tscherniaev, I. I., 114.
 Tschurmanteeva, M. N., 97.
 Taukerman, N. Y., 124.
 Turk, E., 334.
 Turnbull, D., 144.
 Turner, D. L., 206, 212.
 Turner, E. G., 196.
 Turner, F., 115.
 Turner, H. S., 313.
 Turner, W. J., 253, 258.
 Tuttle, L. C., 262.
 Tweedie, M. C. K., 25.
 Twomey, D., 312.
 Twort, F. W., 302, 311.
 Twyman, F., 316.
 Tyndall, A. M., 14.
 Tzukervanik, I. P., 136.
 Ubisch, H. v., 246.
 Udenfriend, S., 276, 287.
 Underhill, S. W. F., 291.
 Ungar, J., 297, 298.
 Urbina, H. E., 106.
 Urey, H. C., 54.
 Urry, W. H., 138, 140, 141,
 146, 150, 152, 153, 160,
 161.
 Usanovitsch, M., 336.
 Usher, F. L., 24.
 Utter, M. F., 260, 265.
 Vajna, F. P., 85.
 Valentiner, S., 94.
 Vanas, D. W., 60.
 Van Cleave, A. B., 110.
 Van Dame, H. C., 332.
 Vandaveer, L., 331.
 Vandembelt, J. M., 229.
 Van den Ende, M., 302.
 Van Heyningen, E. M., 157.
 Vanpee, M., 21, 22.
 Vanselow, A. P., 319.
 Varrallyay, G., 328.
 Vaughan, J. R., jun., 205.
 Vaughan, W. E., 59, 146,
 147, 148, 149.
 Vdovenko, V. M., 97.
 Velden, P. F. van, 99.
 Velghe, C., 22.
 Veltman, P. L., 56.
 Vennesland, B., 239, 265,
 266, 267.
 Vereschtschaguine, L. F.,
 114.
 Vermillion, G., 136.

- Viehweger, H., 102.
 Vincent, G. P., 332.
 Vincent, H. B., 317, 319.
 Vinograd, J. R., 42.
 Vinogradova, E. Y., 126.
 Vischer, E., 275, 281.
 Vives, J. P., 88.
 Voevodsky, V. V., 69, 75.
 Vogler, K., 199.
 Volcani, B. E., 244.
 Volmer, G., 5.

 Wadman, W. H., 273, 281.
 Wadsworth, K. D., 95.
 Waelsh, H., 241, 252.
 Waggaman, W. H., 98.
 Wagner, C. D., 335.
 Wahl, A. C., 117.
 Waksman, S. A., 307, 308.
 Walbank, F., 318.
 Waldmann, H., 176, 177.
 Walen, R. J., 19.
 Walker, H. G., 129.
 Walker, J., 130, 228, 236.
 Walsh, A. D., 59, 114.
 Wallace, A., 329.
 Wallace, G. J., 309.
 Waller, C. W., 226, 227, 230, 231, 233, 237.
 Walsh, A., 317, 322.
 Walters, W. D., 54, 60.
 Walti, R., 319.
 Walton, J. H., 105.
 Wamser, C. A., 93.
 Wandenbulcke, F., 341.
 Wander, I. W., 325.
 Wang, S. N., 58.
 Wannowius, H., 198.
 Ward, A. F. H., 39, 42.
 Ward, E. R., 130.
 Ward, R., 90.
 Wardleworth, J., 208.
 Waring, C. E., 58, 60.
 Waring, C. L., 318.
 Warren, F. L., 136.
 Warrick, E., 60, 63.
 Wartenberg, H. von, 96.
 Wassermann, G., 60.
 Waters, W. A., 51, 139, 155, 158, 159.
 Watkins, W. M., 281.
 Watson, E. R., 219.
 Watson, J. H. L., 23.
 Watt, D., 261.
 Watt, G. W., 102.
 Wattenberg, H., 341.
 Waugh, D. F., 285.
 Webb, D. A., 338.
 Webb, K. R., 109.
 Weber, H. C., 330.
 Weber, L. J., 41.
 Weber, W., 104.
 Webley, D. M., 281.
 Weedon, B. C. L., 134.
 Weedon, W., 328.
 Wegman, T., 290.

 Wegmüller, F., 6.
 Wehrich, R., 326.
 Weijlard, J., 236.
 Weinhouse, S., 96, 263.
 Weisblat, D. I., 235.
 Weiss, C., 294.
 Weiss, C. M., 344.
 Weiss, E., 290.
 Weiss, G., 102.
 Weiss, J., 25, 26, 28, 30, 31, 51, 159, 268.
 Weisz, P. B., 16.
 Weisz-Tabori, E., 266.
 Weitzenböck, R., 196.
 Weizmann, M., 151.
 Weldon, L. H. P., 161.
 Weller, R. A., 279.
 Weller, S., 116.
 Wells, H. G., 292, 295.
 Wells, J. R., 301, 305, 310, 315.
 Wells, R. A., 283.
 Wendt, G. L., 21.
 Wenker, H., 216, 219.
 Wenkert, E., 169.
 Werkman, C. H., 260, 261, 264, 265, 266.
 Werner, A. E. A., 114.
 Wertz, J. E., 55.
 West, J. R., 105.
 West, R., 259.
 West, T. F., 163, 164, 165, 167, 169, 170, 171, 172, 173.
 Westall, R. G., 281, 283.
 Westfall, B. B., 306.
 Westheimer, F. H., 137.
 Westlake, H. E., jun., 105.
 Wheeler, T. S., 83.
 Whitby, (Sir) L., 139.
 White, A., 283, 290.
 White, A. G. C., 261, 264.
 White, D. A., 295.
 White, G. N., 213.
 White, J. F., 332.
 White, L. M., 90.
 Whitehead, C. W., 212.
 Whitlock, M. H., 105.
 Whitman, B., 201.
 Whitmont, F. F., 207, 210.
 Whitmore, F. C., 153, 156.
 Wiberg, E., 86, 92, 93.
 Wick, A. N., 271.
 Wicke, E., 109.
 Wickert, J. N., 35.
 Wicks, Z. W., 86.
 Wiebusch, K. D., 106.
 Wiegand, C. J. W., 129.
 Wieland, K., 91.
 Wieland, T., 280.
 Wienhaus, H., 176.
 Wiken, T., 261.
 Wilber, S., 314.
 Wilcoxon, F., 165, 171.
 Wildman, R. B., 130.
 Wiley, R. H., 131.

 Wilken, J., 317.
 Wilkes, B. G., 35.
 Wilkinson, J. F., 254.
 Wilkinson, S., 275.
 Willan, A., 336.
 Willard, H. H., 98.
 Willbourn, A. H., 68, 69, 70, 71, 72, 73.
 Willemart, A., 134.
 Willgerodt, C., 211.
 Williams, E. F., 287.
 Williams, G., 57.
 Williams, N. T., 15.
 Williams, R. J., 226, 272.
 Williams, R. J. P., 84.
 Williams, T. I., 267.
 Williamson, A. T., 67.
 Willis, H. S., 294.
 Willis, J. B., 107, 114.
 Willstätter, R., 189.
 Wilmarth, W. K., 113.
 Wilson, A. N., 223.
 Wilson, A. S., 116.
 Wilson, C. L., 161, 333.
 Wilson, D. W., 239, 267.
 Wilson, E. G., 339, 340, 341.
 Wilson, G. S., 304.
 Wilson, J., 265.
 Wilson, J. N., 268.
 Wilson, S. H., 320.
 Wilson, T. L., 343.
 Wilson, W., 207.
 Windaus, A., 191, 192, 194.
 Winegard, H. M., 274.
 Winkler, C. A., 58.
 Winkler, F., 259.
 Winnick, T., 242, 243.
 Winslow, A. F., 86.
 Winslow, E. C., 127.
 Winsor, P. A., 37, 38, 43, 44.
 Winsor, R. V., 86.
 Winstein, S., 148.
 Winstein, W. A., 272, 274, 275, 282.
 Winterringham, F. P. W., 334.
 Wintersteiner, O., 286.
 Wirth, H. E., 341, 343.
 Wittenberg, J., 255.
 Witting, R., 341.
 Wittwer, C., 187.
 Woiwod, A. J., 280, 282.
 Wolf, D. E., 199, 223, 232, 233.
 Wolfe, R. A., 323.
 Wolff, J. A., 233.
 Wolfenstein, R., 137.
 Wolfson, M. L., 201, 202, 203, 204, 213, 215.
 Wood, H. G., 241, 243, 261, 263, 265.
 Woodbine, M., 306.
 Woods, D. D., 302.

- | | | |
|---|---------------------------|------------------------------|
| Woodward, R. B., 175, 202. | Wylie, A. W., 115, 116. | Zachariasen, W. H., 116. |
| Woolley, D. W., 214, 289, 302, 311, 313. | Wyss, R., 98. | Zaffaroni, A., 279. |
| Wooster, N., 96. | Yakovlev, B., 77. | Zahl, P. A., 7. |
| Wooster, W. A., 96. | Yamamoto, R., 163. | Zander, H., 130. |
| Work, C. E., 278. | Yanagami, S., 310. | Zappi, E. V., 127. |
| Work, E., 278. | Yanagisawa, J. K., 310. | Zavist, A. F., 157. |
| Work, J. B., 113. | Yanko, W. H., 123. | Zeerleder, A. von, 317, 318. |
| Wormall, A., 301. | Yankwich, P. E., 95, 212. | Zeisel, S., 191. |
| Wormell, T. W., 100. | Yavorsky, P. J., 99. | Zeiss, H. H., 174, 182, 183. |
| Wormser, (Mlle.) Y., 112. | Yeddanapalli, L. M., 60. | Zeldovich, J., 65. |
| Wright, C. P., 306. | Yntema, L. F., 332. | Zetterberg, B., 312. |
| Wright, T. A., 317. | Yost, D. M., 82. | Zomlefer, J., 217, 218. |
| Wuyts, H., 215. | Youmans, A. S., 307. | Zondek, B., 302. |
| Wyatt, G. H., 333, 334. | Youmans, G. P., 304, 307. | Zucker, G., 306. |
| Wyckoff, H. O., 16. | Young, E., 309. | Zumbusch, M., 98. |
| Wyckoff, R. W. G., 10, 82, 275, 278. | Young, E. H. P., 309. | Zwicker, B. M. G., 342. |
| Wyk, A. van der, 46. | Young, W., 331. | Zwicky, R., 186. |
| | Yuill, M. E., 301. | Zwolinski, B. J., 63. |
| | | Zworykin, K., 323. |

INDEX OF SUBJECTS.

- Abietic acid, permanganate oxidation of, 182.
 structure of, 174.
*neo*Abietic acid, 174.
*iso*Abietic acid, 175.
 Acetaldehyde, condensation of, with vinyl cyanide, 125.
 deuterated, thermal decomposition of, 53.
 thermal decomposition of, 52.
 Acetamido-acids, separation of, 276.
 Acetanilide, reduction of, to *cyclohexanone*, 124.
 Acetato-calcium chloride, 90.
 Acetato-lead halides, 98.
 Acetic acid, allyl ester, γ -acetoxybutaldehyde from, 134.
 biochemical function of, 260.
tert.-butyl ester, decomposition of, 60.
 glacial, as solvent in titrations, 335.
 in biosynthesis, 241.
 metabolism of, 260.
 oxidation of, by yeast, 263.
 preparation of, 134.
 reaction of, with acetyl peroxide, 140.
 with selenium dioxide, 159.
 zinc salts, 91.
 Acetic acid, bromo-, reaction of, with oct-1-ene, 153.
 chloro-, and its methyl ester, reaction of, with acetyl peroxide, 140.
dichloro., methyl ester, reaction of, with oct-1-ene, 152.
 chlorothiol- and thiol-derivatives, addition reactions with, 154.
 iodoso-, phenyl ester, methylation by, of aromatic nitro-compounds, 158.
 oximinocyno-, ethyl ester, use of, to liberate amino-acids from their salts, 132.
 Acetone, decomposition of, 58.
 Acetophenone, decomposition of, 58.
 5-Acetoxythiazoles, 209.
 Acetyl chloride, *trichloro.*, reaction of, with oct-1-ene, 152.
peroxide, reactions of, 140.
 with allylbenzene, 161.
 phosphate, 260.
 hydrolysis of, 261.
 Acetylcellulose chromatograms, 270.
 Acetylcholine, synthesis of, in brain extracts, 262.
N-Acetylcolchinel methyl ether, deamination of, 195.
 Acetylene, dimerisation of, 59.
 polymerisation of, 22.
 reactions of, 132.
 reduction of, to ethylene, 123.
 Acetylenediureide, hydroxy-, 251.
 Acetylenic compounds, 132.
N-Acetyliodocolchinel methyl ether, degradation of, 193.
 Acetylmethylcarbinol, formation of, by yeast, 264.
 Acetyloleanolic acid, conversion of, into β -amyrin acetate, 205.
 Acetylpeptides, separation of, 276.
 Acid chlorides, reduction of, 122.
 Acid-fastness of bacilli, 297.
 Acids and their derivatives, 128.
 carboxylic, synthesis of, 134.
 conversion of, into alcohols by thiol-esters, 205.
 fatty, effect of aggregation on properties of, 50.
 separation of, 277.
 mineral, removal of, from polysaccharide or protein hydrolysates, 132.
 organic, separation and detection of, 282.
 standardisation of, 331.
 strong, separation of, from weak acids, 132.
 weak, titration of, in non-aqueous solvents, 335.
 Acetaldehyde, addition of methylthiol to, 130.
 Acrylic acid, ethyl ester, β -carbethoxypropaldehyde from, 134.
 methyl ester, reaction of, with thiols, 154.
 reaction of, with diazonium salts, 155.
 Acrylonitrile. *See* Vinyl cyanide.
 Actinons, 115.
 Acylation, 129.
 Addition reactions, 149.
 Adenine, preparation of, from 2-mercaptoadenine, 205.
 Adenines, incorporation of, into tissue purines, 246.
 Adenosine phosphates, synthesis of, 138.
 Adenylic acid, muscle, deamination-reamination of, 246.
 Adrenaline, separation of, 282.
 Adsorption on carrier material, 271.
Aerobacter, acetic acid as carbon source for, 260.
 Aerosols, 35.
 Aerosol I.B., critical concentration in solutions of, 38.
 Aerosol O.T., copper and nickel salts, 36.
 critical concentration in solutions of, 38.
 transition to aggregated state in, 42.
 Air, detn. of ammonia in, 341.
 Agathic acid, structure of, 184.
 Aggregation in ionisation reactions, 17.
 Alanine, conversion of, into 2:4:5-trimethyloxazole, 131.

- β -Alanine, preparation of, 125.
 Alcohols, action of rays on, 22.
 secondary, oxidation of, to ketones, 124.
 Aldehyde groups, protection of, 213.
 Aldehydes, aromatic, preparation of, 214.
 heating of, with ammonium formate, 129.
 preparation of, from thiol-esters, 204.
 reduction of, 122.
 Alepic acid, 174.
 Alkaloids, solanaceous, separation of, 278.
 5-Alkoxyoxazoles, 210.
 Alkylation, 135.
 Alkylbenzenesulphonates, conductivity in solutions of, 38.
 3-Alkyl-naphthaquinones, 2-hydroxy-, preparation of, 142.
 Alkyltrimethylammonium bromides, conductivity in solutions of, 38.
 Allantoin, 251.
 Allyl alcohol, γ -hydroxybutaldehyde from, 134.
 Allylbenzene, reaction of, with acetyl peroxide, 142, 161.
 Alopecia, inositol as nutritional factor in, 313.
 Aluminium chloride, compound of, with ammonia, 94.
 hydrolysis of, 94.
 fluoride, compounds of, with ammonia, 93.
 oxide, precipitation of, from sodium aluminate solutions, 94.
 phosphide, preparation of, 93.
 sulphate, compounds of, with ammonia, 93.
 Amides, preparation of, 128.
 Amidines, preparation of, 127, 128.
 Amines, aliphatic long-chain, acid-binding properties of, 132.
 aromatic, phosphorylation of, 138.
 potentiometric titration of, 335.
 synthesis of, 129.
 Amino-acids, 130.
 detection of, in chromatograms, 274.
 of insulin, 286, 287.
 quantitative chromatography of, 279.
 removal of salts from solutions of, 273.
 separation of, 276, 278.
 thiobenzoylation of, 208.
 titration of, in non-aqueous solvents, 336.
 water-soluble, preparation of, from their salts, 132.
 α -Amino-acids, conversion of, into oxazoles, 131.
 differentiation of, 275.
 preparation of, 215.
 D -Amino-acids, distinction of, from L -amino-acids, 275.
 ω -Amino-acids, preparation of, 128.
 α -Amino-esters, acylation of with S -phenyl chlorothioformate, 213.
 Amino-groups, protection of, 213.
 Aminomethylation, 136.
 Amino-sugars, detection of, in chromatograms, 274.
 Ammonia, decomposition of, by α -rays, 19.
 by X-rays in xenon, 21.
 detn. of, in sea water, 341.
 liquid, solutions of metals in, 99.
 oxidation of, 99.
 reactions of, with nitrogen oxides, 99.
 Ammonium carbamate, dissociation pressure of, 99.
 dichromate, thermal dissociation of, mixed with ammonium sulphate, 99.
 fluoride, fused, electrolysis of, 101.
 molybdate, composition of, 108.
 nitrite from ammonia oxidation, 99.
 salts, effect of ultra-violet light on solutions of, 99.
 Amphipathic agents, 34.
 Amphiphilic property, 43.
tert.-Amyl peroxide, 146.
 β -Amyrin acetate, 205.
 Anæmia, pernicious, separation of anti-substance for, 278.
 Analysis, coulometric, 336.
 emission spectrographic, 316.
 volumetric, 330.
 apparatus for, 333.
 Anhydro-sugars, preparation of, 214.
 2-Anilino-4- δ -diethylamino- α -methylbutyl amino-6-methylpyrimidine, 2-*p*-chloro-, derivatives, chemotherapy with, in tuberculosis, 307.
 Anisole, additive compounds of, with germanium, silicon, and tin chlorides, 97.
 o -substitution in, 158.
 Anisotropy, optical, 49.
 Anthocyanins, separation of, 282.
 Anthranilic acid, reduction of, to o -aminobenzyl alcohol, 123.
 Antibiotics for control of tuberculosis, 307.
 Antigens, artificial, against tubercle bacilli, 301.
 Antimonic acid, 102.
 Antimony pentachloride, molecular compounds of, with acid chlorides, 102.
 Antipyrine, lanthanon complexes with, 115.
 Antiseptics, effect of phospholipoids on toxicity of, 303.
 Arginine, detection of, in chromatograms, 274.
 Argon, liquid, ionisation of, by α -rays, 13.
 value of W for γ -rays in, 13.
 Arsenic, detn. of, 337.
 in sea water, 340.
 trihydride, liquid, density of, 102.
 trioxide as volumetric standard, 332.
 solubility of, 102.
 Arsine. *See* Arsenic trihydride.
 Arsonium salts, synthesis of, 138.
 Aryldiazonium salts, 130.
 Arylfurans, 158.
 Arylstibonic acids, 102.
 Asparagus, sulphur compound from, 201.
 DL-Aspartic acid, 131.
 Atmosphere, dinitrogen oxide in, 100.
 helium content of, 85.

- Atoms, identification of, 16.
 Atomic energy, reports on, 84.
 Atomic weight of boron, 92.
 Atomiser, metal, 328.
 Auger effect, 11.
 Aziridines, 216.
 Azobenzene, solubility of, in cetylpyridinium chloride and in hexadecane, 41.
 Azo-compounds, decomposition of, 56.
 Azoles, 206.
 Azulene, structure of, 187.
 BCG, vaccine treatment with, in tuberculosis, 300.
 Bacilli, inositol synthesis by, 313.
 John's, leprosy, timothy-grass, and tubercle, 310.
 leprosy and timothy-grass, acids from, 297.
 timothy-grass, growth factor from, 311.
 tubercle, chemical composition of, 295.
 effect of acids and bases on, 303.
 growth inhibitors for, 312.
 mode of action of, 295.
 Bacteria, amino-acids in, 278.
 Bacteriophage, inactivation of, by X-rays, 31.
 Barium azide, impact detonation of, 19.
 iron oxide, structure of, 90.
 titanium oxide, 90.
 Baudisch reaction, 137.
 Beef, digestion of, 279.
 ethanolamine- and hydroxylysine-phosphoric acids in, 279.
 Benzaldehyde, reaction of, with *tert*-butyl peroxide, 148.
 Benzene, chloromethylation of, 136.
 consolation of water and, by sodium oleate, 43.
 nitration of, 137.
 oxynitration of, 137.
 reaction of, with methyl alcohol or methyl ether in presence of catalysts, 135.
 solubility of, in cetylpyridinium chloride, 40.
 Benzene, bromo-, reaction of, with *n*-butylmagnesium bromide, 160.
 Benzoic acid, reduction of, to benzyl alcohol, 123.
 sodium salt, solubility of organic substances in, 41.
 Benzoic acid, *p*-amino-, antibacterial action of, 307.
 o-chloro-, as volumetric standard, 330.
 Benzopyrylium salts, synthesis of, 133.
 Benzoyl peroxide, kinetics of decomposition of, in solvents, 143.
 reaction of, with ethers, 143.
 with methyl maleate, 155.
N-Benzoylcolchide, 194.
N-Benzoylcolchicine anhydride, 194.
 Benzoylrhizopterin, 232.
 5-Benzoyl-2 : 3 : 4-triacetyl-L-arabinose, 214.
 Benzyl chloride from chloromethylation of benzene, 136.
 cyanide, reaction of, with formamide, 127.
 hyponitrite as polymerisation catalyst, 158.
 sulphide, reaction of, in ethanol with Raney nickel, 199.
 2-Benzyl-4-hydroxymethylenethiazol-5-one, 210.
 Benzylideneazaine, decomposition of, 57.
 4-Benzylidenethiazolone, 209.
 2-Benzyl-4-*p*-methoxybenzylthiazol-5-one, 209.
 Benzylpenicillin, structure and stereochemistry of, 200.
 Benzylpenillamine, synthesis of, 209.
 β -(Benzylsulphonamido)propionic acid, 125.
 Beryllium carbonate, basic, dissociation of, 89.
 hydride, 122.
 nitrate, dissociation of, 89.
 sulphate, dissociation of, 89.
 sulphide, preparation of, 89.
 tetracyanonickelate, 114.
 Biological extracts, flame photometry with, 329, 330.
 Biosynthesis, function of small molecules in, 239.
 Biotin, stereoisomers of, 220, 221.
 β -Biotin, 220.
 structure of, 199.
 (\pm)-Biotin, 223.
 (\pm)-*epi*Biotin, 221, 224.
 (\pm)-*epiallo*Biotin, 223.
 Bismuth, preparation of bismuthates from, 103.
 Bismuth triiodide, reaction of, with sodium in liquid ammonia, 102.
 Blood, hæmin isolation from, 259.
 spectrographic analysis of, 325.
 taurine in, 279.
 Blood-corpuses, red, hæmoglobin synthesis in, 259.
 Blood group A substance, 281.
 Borax, pH of 0.05M., 333.
 Borazene derivatives, dimerisation of, 93.
 Borazine derivatives, trimerisation of, 93.
 Borazole, and its derivatives, 93.
 Boric acid, detn. of, volumetrically, 336.
 Boron, atomic weight of, 92.
 isotopes, 92.
 detn. of, 330.
 fluoride ammoniates, 93.
 as catalyst in ketone synthesis, 129.
 nitride, 93.
 Bouveault-Blanc reaction, 123.
 Brain extracts, acetylcholine synthesis in, 262.
 Bremstrahlung, 11.
 Bromine, colour of, at low temperatures, 110.
 generation of, in coulometry, 337.
 Bromoform, addition reactions of, 151.

- Buffers added to partition chromatograms, 270.
 Buffer solutions as pH standards, 333.
 Burettes, 333, 334.
 Butadiene from vinylacetylene reduction, 124.
 sulphone. *See* 2:5-Dihydrothiophen 1:1-dioxide.
 vinyl cyanide addition to, 126.
n-Butane, decomposition of, 58, 59.
*iso*Butane, decomposition of, 60.
tert-Butyl hydroperoxide, 146.
 peroxide, kinetics of pyrolysis of, 146.
 reactions of, 145.
n-Butylmagnesium bromide, reaction of, with bromobenzene, 160.
 8- and 9-*D*-*arabo*Butylpteridines, 2-amino-6-hydroxy-8- and -9-*tetra*hydroxy-, 235, 236.
 Butyric acid, α -amino-, in animal and plant extracts, 279.
 γ -amino-, in potatoes, 279.
*iso*Butyric acid, *dichloro*-, preparation of, from 1-methylallyl cyanide, 125.
 $\beta\beta'$ -*dimercapto*-, 201.
*iso*Butyrophenone, Willgerodt-Kindler reaction with, 213.
*iso*Butyryl chloride, reaction of, with acetyl peroxide, 140, 141.

 Cadaverine from pentamethylene dibromide, 130.
 Cadmium hexachloroaurate, 89.
 hydroxide, precipitation of, 91.
 iodide, thermal dissociation of, 91.
 sulphates, basic, 91.
 tetracyanonickelate, 114.
 Cæsium chloride, reaction vessels coated with, 68.
 fluoride vapour as mineraliser, 96.
 hydrogen fluorides, 86.
 hydroxide, cell for preparation of, 86.
 rhodium chlorides, complex, 115.
 Calciferol, effect of, on tuberculosis, 313.
 Calcification in caseous areas, 294.
 Calcium aluminate, 90.
 carbonate, thermal decomposition of, 89.
 detn. of, 330.
 hydride, preparation and industrial uses of, 89.
 hydroxide, chlorination of, 89.
 oxides, 89.
 phosphate carbonates, complex, 90.
 Calculators for emission spectrography, 319.
 Carbohydrates, chromatographic separation of, 281.
 detection of, in chromatograms, 274.
 Carbon, combustion of, in air, 95.
 comparison of, with silicon, 96.
 detn. of, in sea water, 343.
 isotopes, 94, 95.
 Carbon *tetrachloride*, reaction of, with α - and β -naphthoyl peroxides, 141.
 fluorides, 95.
 Carbon halides, addition reactions of, with ethylenic compounds, 150.
 monoxide, oxidation of, 21.
 preparation of, 96.
 solution of, in ammoniacal copper (I) chloride, 87.
 use of, in organic synthesis, 134.
 dioxide, assimilation of, heterotrophic, 266.
 reduction of, to methyl alcohol, 123.
 utilisation of, by animals, 267.
 in biosynthesis, 239, 265.
 Carbonyl chloride, synthesis of, 21.
 chlorofluoride, 96.
 cyanide, 96.
 halides, 96.
 selenide, 96.
 telluride, 96.
 Carbonylation, 133.
 3-Carboxy-6-methylpyrazine, 2-amino-, 236.
 Carboxypeptidase, irradiation of solutions containing, 25.
 Car-3-ene, oxidation of, 163.
 Caseation, 293.
 Casein, digestion of, 279.
 Catalysts for acetylenic reduction, 123, 124.
 for addition of carbon monoxide, 134.
 Cedar wood, constituents of, 189.
 Cells, electrochemical, Castner-Kellner, 86.
 laboratory, 109.
 photo-electric, multiplier, 323.
 Cellulose from marine algae, 281.
 Cement, spectrographic analysis of, 325.
 Cepharanthine, chemotherapy with, 309.
 Cerium oxides, 115.
 Cetylpyridinium chloride, conductivity in solutions of, 39.
 solubility of azobenzene in, 41.
 solubility of benzene in, 40.
 micelle, radius of, 49.
 Chains, initiation of, in reactions, 73.
 Charge neutralisation, 15.
 Chaulmoogra oil, treatment with, of leprosy, 314.
 Chaulmoogric acid, structure of, 314.
 Chelate compounds, synthetic, 113.
 Chloramine-T, 332.
Chlorella, chromatography of photo-synthesis by, 275.
 Chlorine fluorides, 109.
 isotopes, 110.
 dioxide, preparation of, 110.
N-Chloroamides, catalytic action of, 155.
 Chlorocobalt (+1) trichlorocobaltate, 112.
 Chloroform, addition reactions of, 151.
 irradiation of, 22.
 titrations of alkaloïds in, 335.
 Chloromethylation, 136.
 Cholesterol, biosynthesis of, 262.
 fatty-acid excretion after feeding on, 314.
 Choline, detection of, in chromatograms, 275.

- Choline-esterase, fluorophosphonates as inhibitors of, 139.
- Chroman derivatives, synthesis of, 125.
- Chromatograms, paper, detection of substances on, 273.
- partition, 269.
- Chromatography, partition, 267.
- apparatus for, 272.
- in inorganic chemistry, 84.
- principles of, 268.
- Chromium, electrodeposition of, from complexes, 107.
- trioxide, oxidation by, 159.
- reduction of, by hydrogen, 107.
- Chromium(II) chloride as catalyst in reduction of acetylene, 123.
- iodide, hydrazine complexes of, 107.
- Chromium(III) chloride, green and violet, 107.
- sulphate, green and violet, 107.
- Chromobacterium indium*, dye from, 311.
- Chrysanthemumcarboxylic acids, 163.
- Chrysanthemum cinerariifolium*, 162.
- Chrysanthemumdicarboxylic acid, structure of, 172.
- Chrysanthemummonocarboxylic acid, structure of, 171.
- Chymotrypsin, insulin digestion with, 290.
- Cinchona alkaloids, titration of, in chloroform, 335.
- Cinerins, formulæ of, 162.
- Cinerosolone, 163, 167, 171.
- Cinerone, 171.
- Cinnamic acid, reduction of, to 3-phenylpropyl alcohol, 123.
- Cinnamyl chloride, reaction of, with Grignard reagents in presence of cobalt chloride, 161.
- Citraconic acid, reaction of, with diazonium salts, 155.
- Citrulline, 252.
- Clays, montmorillonite, hydration of, 45.
- Clostridium butylicum*, co-enzyme A in, 262.
- Clostridium cylindrosporum*, breakdown of uric acid by, 252.
- Clostridium kluyveri*, acetyl phosphate from reactions of, 260.
- Cluster theory, 18.
- "Clusters" in gases, 14.
- Coating of reaction vessels, 68.
- Cobalt compounds, complex, 113.
- hydride, 111, 112.
- Cobalt(II) chloride solutions, 112.
- hydroxide, oxidation of, 112.
- Co-enzyme A, 262.
- Colchicine, 191.
- Colchicine, and its derivatives, 187.
- biological effects of, 190.
- oxidation of, 194.
- iso*Colchicine, 191.
- Colchicinol methyl ether, oxidation of, 194.
- structure of, 194.
- Combination reactions, 27.
- Comets, carbon isotopes in spectra of, 94.
- Complex anions, cryscopy with, 108.
- Compounds, complex, stability of, 84.
- Compton scattering, 11.
- Co-ordination compounds, 82, 83.
- Copal. *See under* Resins.
- Copper arsenates, 86.
- carbonyl, attempt to prepare, 87.
- chromates, 88.
- compounds, chelate, stability of, and their reduction in pyridine, 84.
- detn. of, in sea-water, 344.
- oxidation of, 86.
- pyrophosphates, ethylenediamine complexes with, 88.
- sulphides, 86.
- Copper(I) chloride, ammoniacal solution, solution of carbon monoxide in, 87.
- cyanide, complex nature of, 87.
- hydroxide, structure of, 86.
- salts, 86.
- Copper(II) chloride, solutions of, 87.
- nitrites, hydrated, 88.
- salts, basic, 87.
- Corynebacterium*, fermentation factor in cultures of, 229.
- Coulometer, hydrogen-oxygen, 337.
- Coulometric analysis, 336.
- Coulometry, 336.
- Creatine, chromatography of, 282.
- Creatinine, chromatography of, 282.
- detection of, in chromatograms, 274.
- Crotonaldehyde, reduction of, to crotyl alcohol, 123.
- Crotonic acid, ethyl ester, ethyl β -formylbutyrate from, 134.
- Cryptomeria japonica*, cryptopimaric acid from, 180.
- Cryptopimaric acid, 180.
- Cryptopinone, 180.
- Cyanides, preparation of, 126.
- reaction of, with formaldehyde, 128.
- di*Cyanides, reduction of, 128.
- Cyanoethylation, 124.
- Cyanogen chloride, 110.
- treatment of acids or salts with, 127.
- Cyclotron, 6.
- D.F.P. *See* Diisopropyl fluorophosphonate.
- Dacrydium biforme* and *kirkii*, acids from, 180.
- Deaminocolchicinol methyl ether, 193.
- Deaminocolchicinol methyl ether, iodo-, degradation of, 194.
- iso*Deaminocolchicinol methyl ether, 193.
- Deaminorhizopterin, 232.
- Deaminoisoxanthopterincarboxylic acid, 234.
- cis*-Decalin, structure of, 183.
- Dehydroabietane, 6-hydroxy-, 182.
- Dehydroabietic acid, 176.
- structure of, 182.
- Dehydroabietinol, 6-hydroxy-, oestrogenic activity of, 182.
- Dehydroperillic acid, 189.
- 2-Deoxy-D-allitol, 203.

- Deoxycholic acid, adsorption properties and structure of, 42.
 sodium salt, transition to aggregated state in, 42.
- 1-Deoxy-D-galactitol penta-acetate, 203.
- Deoxyhexoses, synthesis of, 203.
- Deoxypentose, synthesis of, 203.
- Deoxy-sugar alcohols, synthesis of, 202.
- Dethiobenzylpenicillin, 200.
- Dethiobiotin methyl ester, 199.
- Dextropimaric acid, structure of, 178.
- iso*Dextropimarinal, 180.
- Diacetyl, pyrolysis of, free radicals from, 54.
- Diamond, structure and synthesis of, 95.
- Di-*tert*.-amyl peroxide, decomposition of, 60.
- Diazo-compounds, aromatic, aryl radicals from, 158.
 for polymerisation, 157.
- Diazomethane, methylation with, 135.
 reaction of, with phenyl *isocyanato*, 131.
- Diazone, chemotherapy with, in tuberculosis, 306.
- Diazonium salts, reaction of, with olefinic acids, 155.
- Dibenzocyclohepta-3 : 5-dienes, 196.
- Dibenzocyclohepta-1 : 3 : 5-trienes, 195.
- Dibenznorcaradienecarboxylic acid, 198.
- Dibenzotropolone, 197.
- 3 : 6-Dibenzyl-1 : 2 : 4 : 5-tetrazine, 208.
- Di-*tert*.-butyl peroxide, decomposition of, 59.
- NN'*-Di-*n*-butylurea, 201.
- Dicarbonyl copper(I) bromide and chloride, 87.
- n*- and *iso*-Dicinnamyls, 142, 143.
- Dicobalt octacarbonyl as catalyst, 134.
- Dideuteracetylene, polymerisation of, 22.
- p*-Dideutero benzene, 161.
- Diethylamine, *di*-2-cyano-, 125.
- Diethylarsine, *di*-2-cyano-, 126.
- NN*-Diethylbenzylsulphonamide, *NN*-*di*-2-cyano-, 125.
- Diethyl cellosolve. *See* Ethylene glycol diethyl ether.
- Diethyl ether. *See* Ethyl ether.
- Difluorenyl trisulphide, structure of, 201.
- Digermane, decomposition of, 60.
- Diguanidines, synthesis of, 215.
- $\alpha\alpha'$ -Di-*n*-heptylsuccinic acid, half-ester, chemotherapy with, 314.
- Dihydroabietic acids, 177.
- Dihydrocinerolone, 167.
- Dihydrocinerone, 167.
- Dihydroglyoxalines, synthesis of, 127.
- Dihydropimaric acid, 178.
- 7 : 10-Dihydropteridine, 228.
- Dihydropteroylglutamic acid, 229.
- Dihydrostreptomycin, chemotherapy with, in tuberculosis, 308.
- 2 : 5-Dihydrothiophen 1 : 1-dioxide, reaction of, with trichlorobromomethane, 162.
- 7 : 10-Dihydroxanthopterin, 228.
- 4 : 5-Diketo-2-benzylidone-1 : 3-dithiolan, 208.
- 1 : 4-Diketones, synthesis of, 141.
- Dimethylaminoazobenzene, critical concentration of, in soaps, 42.
- Dimethylaminobenzaldehyde as reagent for tryptophan, 274.
- 2 : 3-Dimethylbutane, reaction of, with *tert*.-butyl peroxide, 147.
- Dimethyldialkylammonium salts, aggregation in, 37.
- 2 : 2-Dimethylethyleneimine, polymerisation of, 217.
 preparation of, 217.
- Dimethylgermanium oxide and sulphide, 97.
- Dimethylglyoxime, metallic complexes with, 85.
- Dimethylglyoximorhodium polysulphides, 115.
- 3 : 6-Dimethylpyrazine, 2-hydroxy-, 214.
- Dinitrogen monoxide, decomposition of, by α -rays, 15.
 production of, 100.
 dioxide, effect of, on hydrogen-oxygen reaction, 77.
 on reaction rate, 52, 58.
 oxidation of, by nitric acid vapour, 55.
 rate of decomposition of, 65.
 reactions of, with the halogens and with oxygen, 54.
 pentoxide, action of hydrogen peroxide on, 100.
 heat of solution of, in water, 100.
 vapour, thermal decomposition of, 55.
- Dinitrosulphurous acid, salts, 106.
- 1 : 4-Dioctyloxybenzene-3-sulphonic acid, potassium salt, 36.
- 1 : 3-Dioctyloxybenzene-4-sulphonic acid, potassium salt, 36.
- cis*-Diols, formation of, from ethylenic compounds, 198.
- Dioxan, reaction of, with benzoyl peroxide, 143.
- Dioxanyl radical, 155.
- Diphenylamine, 2-amino-, red base from, antiseptic to tubercle bacilli, 312.
- 2 : 3-Diphenylbutane from ethylbenzene, 141.
- 2 : 3-Diphenyl-2 : 3-dimethylbutane from *isopropyl*benzene, 141.
- Diphenyl ether, additive compounds of, with germanium, silicon, and tin chlorides, 97.
- s*-Diphenylethylene glycol dibenzoate, 148.
- s*-Diphenylguanidine as volumetric standard, 331.
- Diphenyliodonium chloride, decomposition of, in presence of pyridine, 158.
- Diphenyl sulphone, hydrogenolysis of, 200.
- Diphenyl sulphone, *diamino*-, antibacterial action of, on tubercle bacilli, 305.
- Diphenyl sulfoxide, hydrogenolysis of, 200.

- Diphenylpropionic acid, Friedel-Crafts cyclisation of, 197.
- Diphtheria, flavin production in, 282.
- Diisopropyl fluorophosphate, 139.
- 2 : 2'-Dipyridyl in sea water analysis, 344.
- Dipyrromethines, aldehyde synthesis of, 258.
- Disilane, thermal decomposition of, 96.
- Distrychnidyl as reagent for nitrates, 342.
- Diterpenes, 174.
- Dithiobenzoic acid, carboxymethyl ester, thiobenzoylation with, 208.
- Dithioformic acid, storage of, as potassium salt, 208.
- Dithio-*n*-hexoic acid, methyl ester, thioacylation with, 208.
- use of, for preparation of thioacylamido-acids, 207.
- Dithionic acid, structure of, 104.
- 2 : 5-Dithionipiperazine, 207.
- Dithio-oxamide in chromatography, 281.
- Dithiophenylacetic acid, methyl ester, thioacylation with, 208.
- storage of, as potassium salt, 208.
- use of, for preparation of thioacylamido-acids, 207.
- oo'*-Ditolyl, *oo'*-*di*bromo-, condensation of, with malonic ester, 196.
- Dosimeters, 10.
- Dosimetry, 8.
- Drying, intensive, 54.
- Dyes, Turkey-red oil as solvent for, 42.
- Dynamic state of body constituents, 239.
- Earth, age of, from lead isotope abundance, 97.
- Earths, rare, in filters for flame photometry, 328.
- Electrodes, casting technique for, 320.
- for emission spectrography, 318.
- gas, 6.
- Electrolysis, coulometer for indicating progress in, 337.
- Element 61, 83.
- Embelin, 142.
- Emulsifying agents, 34.
- Emulsions, X-ray structure of, 48.
- Energy absorption, mechanism of, 10.
- activation, for nitric oxide decomposition, 66.
- relation of, to vibration frequency, 63.
- mean, to create ion pairs, 12.
- Epichlorohydrin, reaction of, with sodium acetylide in liquid ammonia, 133.
- Ergosterol, inactivated, effect of, on tuberculosis, 313.
- Escherichia*, acetic acid as carbon source for, 260.
- Esters, reduction of, 122.
- Esterification, 128.
- Ethane, photochemical bromination of, 65.
- Ethane, 1 : 1- and 1 : 2-dichloro-, dehydrochlorination of, 60.
- Ethanolamine, metallic complexes with, 85.
- Ethers, decomposition of, 56.
- reaction of, with benzoyl peroxide, 143.
- 5-Ethoxy-2-benzylthiazoline, 210.
- Ethyl alcohol, phosphorylation of, 138.
- Ethyl alcohol, 2-amino-, 2-acetyl derivative, 219.
- Ethyl chloride, dehydrochlorination of, 60.
- cyanide, 2-chloro-, 125.
- ether, decomposition of, 57.
- reaction of, with benzoyl peroxide, 143.
- vinyl ether, decomposition of, 58.
- Ethylamine, 2-cyano-, 125.
- hydrolysis of, to β -alanine, 125.
- Ethylaminotrimethylborons, 93.
- Ethylbenzene, dissolved in potassium laurate, density of, 51.
- oxidation of, by air, 159.
- reaction of, with acetyl peroxide, 141.
- Ethylene, hydrogen chloride addition to, 149.
- reaction of, with sulphur, 105.
- Ethylene, *cis*- and *trans*-1 : 2-dicyano-, reaction of, with cyclopentadiene, 127.
- Ethylene cyanide, 125.
- cyanohydrin, cyanoethylation with, 125.
- glycol, solubilisation in, 44.
- diethyl ether, reaction of, with benzoyl peroxide, 143.
- oxide, reaction of, with phosphorus trihalides, 138.
- Ethylenediamine, complexes of, with copper pyrophosphates, 88.
- mercury(II) complexes with, 92.
- Ethylenediaminoheteropolymolybdates, 108.
- Ethylenediaminoheteropolytungstates, 108.
- Ethylenedithiol, condensation of, with 3 : 7 : 12-triketocholanic acid, 201.
- Ethyleneimine, polymerisation of, and industrial uses of products, 216.
- preparation of, 216.
- reaction of, with acetic acid, 218.
- Ethyleneimines, conversion of, into ethylenediamines, 217.
- trisubstituted, 217.
- Ethyleneimine ketones, 219.
- Ethyleneiminyllithium, 219.
- Ethylene compounds, addition reactions of, with halogenomethanes, 150.
- conversion of, into *cis*-diols, 198.
- 2-Ethylethyleneimine, conversion of, into 1 : 2-butylenediamine, 218.
- Ethylmercury phosphates, 92.
- Ethylpentachlorobenzene, α -bromination and β -chlorination of, 157.
- Ethyltrichlorosilane, chlorination of, 156.
- Ethynylation, 132.
- Ethynyl ketones, reaction of, with phenols, 134.
- Europium, at. wt. and isotopes of, 115.
- Excitation sources for emission spectrography, 321.

- Explosions, limits of, in hydrogen-oxygen reaction, 70, 71.
 Explosive, from hydrogen peroxide and manganese dioxide, 104.
 Explosives, mixed, nitrogen oxidation in, 65.
 Ferric oxide, action of chlorine on, 110.
 Ferrous ethylenediamine sulphate, 333.
 sulphate, oxidation of solutions of, by rays, 31.
 Ferruginol, 182.
 Fertilisers, spectrographic analysis of, 324.
 Filters for flame photometry, 327, 328.
 Flame technique in spectrography, 325.
 Flavin adenine dinucleotide, 245.
 separation of, from tissues, 282.
 Flavins, detection of, in chromatograms, 274.
 Fluorescence in chromatography, 274.
 Fluorides, non-metallic, preparation, properties and structure of, 109.
 Fluorine, chemistry of, symposium, 109.
 isolation of, 109.
 perchlorate, 109.
 ω -Fluoro-acids, carboxylic long-chain, preparation of, 126.
 Fluoroaminophosphine oxides, 139.
 Fluorophosphonic acid, derivatives, 138.
 Fluorophosphoric acid, 102.
 Formaldehyde, reaction of, with cyanides, 128.
 with insulin, 291.
 Formaldoxime, decomposition of, 59.
 Formamide, reaction of, with benzyl cyanide, 127.
 Formamides, reduction of, with Raney nickel, 124.
 Formamidines, disubstituted, preparation of, from thioureas, 206.
 Formic acid, copper and silver salts, decomposition of, 87.
 isopropyl ester, decomposition of, 60.
 Foods, spectrographic analysis of, 325.
 Foundry control, spectrography in, 326.
 Fruits, separation of acids from, 277.
 Fumaric acid, detn. of, in tissues, 277.
 diethyl ester, diethyl α -formylsuccinate from, 134.
 Furan, acylation of, 129.
 Gadolinium, at. wt. and isotopes of, 115.
 Galls, colouring matters of, 189.
 Gallium tetracyanonickelate, 114.
 Gas electrodes, 6.
 masks, activated silver oxide for, 88.
 reactions, thermal homogeneous, 51.
 Gases, values of W for, 13.
 Generator, van der Graaff, 6.
 Germanic acid, 97.
 Germanium hydrides, 97.
 Germanomolybdic acid, 109.
 Germanotungstic acid, 109.
 D-Glucose, quinovose tetra-acetate from, 204.
 Glutamic acid, detn. of, 277.
 DL-Glutamic acid, 131.
 Glutathione, uptake of glycine into, 241.
 Glycine, condensation of, with pyruvic acid, 256.
 decomposition of, by *Diplococcus glycinophilus*, 244.
 in porphyrin biosynthesis, 253.
 metabolic activity of, 241.
 oxidation of, in the body, 244.
 properties of, 241.
 Glycine oxidase, 244.
 Glycogen, formation of, from glycine, 243.
 liver, conversion of acetic and butyric acids into, 263.
 Glycols, chloromethylation of, 136.
 1 : 2-Glycols, titrations in, 335.
 Glycyl-isoleucyl-valyl-glutamic acid, 289.
 Glyoxal tetra-acetate, decomposition of, 60.
 Glyoxalines, *mono*- and *di*-mercapto-, desulphurisation of, 206.
 Glyoxaline-4(5)-carboxyamides, 5(4)-amino-, 250.
 Glyoximocobalt(III) polysulphides, 113.
 Gold, quantitative precipitation of, 88.
 Gold telluride, 89.
 Gomberg reaction, 157.
 Gramicidin S, chromatography with, 277.
 structure of, 279.
 Granulomata, tubercle-like, synthetic substances producing, 298.
 Graphite oxide, 95.
 Graphitic acid, salts, 95.
 Grignard reactions with lithium and magnesium, 86.
 Grignard reagents, reactions of, in presence of metallic halides, 160.
 Growth factors for bacilli, 311.
 Guanidines, synthesis of, 215.
 Hæm, *in vitro* synthesis of, 254.
 Hæmatoporphyrin dimethyl ether, preparation and oxidation of, 255.
 Hæmin from blood, 259.
 Hæmoglobin, chromatography with, 277.
 synthesis of, in red blood cells, 259.
 Hafnium, separation of, from aluminium, 98.
 from zirconium, 98.
 Hair, medullated, amino-acids in, 278.
 Halogen atoms, reactions of, 155.
 Helium isotopes, separation of, 85.
 sources of, 85.
 n-Heptane, decomposition of, 60.
 dissolved in potassium laurate, density of, 51.
 Heterocyclic compounds, 216.
 synthesis of, 209.
 Hexachloroaurates, isomorphism of, 89.
 Hexahydrocolchicine, 191.
 Hexahydrocolchicine, 191.
 Hexahydropyretetrone, 166.
 Hexahydro-s-triazines, 128.
 Hexane, solubility of, in sodium oleate solution, 40.
 cycloHexane, decomposition of, 60.

- cyclo*Hexane, *hexachloro*-, commercial, separation of, 278.
*meso*Hexane-1 : 3 : 4 : 6-tetraol, 203.
*cyclo*Hexene, decomposition of, 60.
*cyclo*Hex-3-ene, 1-cyano-, 126.
Hexæstrol methyl ether from *p*-methoxy-*n*-propylbenzene, 141.
Hippuric acid, *p*-amino-, synthesis of, 242.
Histamine, detection of, in chromatograms, 274.
Histidine, detection of, in chromatograms, 274.
Hydnocarpic acid, structure of, 314.
Hydrazine, action of α -rays on, 21.
detn. of, coulometrically, 336.
Hydrazobenzene, hydrogenolysis of, in ethanol, 199.
Hydrazoic acid, action of active nitrogen on, 99.
Hydrides, 86.
preparation of, 122.
Hydriodic acid. *See* Hydrogen iodide.
Hydroborons, 92.
Hydrobromic acid. *See* Hydrogen bromide.
Hydrocarbons, aromatic, acylation of, 129.
catalysed gas-phase reactions of, 135.
pyrolysis of, 60.
Hydrochloric acid, standardisation of, 336.
See also Hydrogen chloride.
Hydrocyanic acid. *See* Hydrogen cyanide.
Hydrofluoric acid. *See* Hydrogen fluoride.
Hydrogen, action of, on soot, 95.
atoms, generation of, in water, 29.
identification of, 16.
explosive combination of, with oxygen, 104.
isomerisation of, by α -rays, 20.
isotopes, separation of, 86.
liquid, plant for, at Oxford, 86.
ortho- and para-, separation of, 85.
para-, decomposition of, by α -rays, 20.
reaction of, with oxygen, 67, 69.
with sulphur, 105.
Hydrogen bromide, addition of, to olefinic compounds, 149.
formation of, from its elements, 21.
chloride, addition of, to ethylene and propylene, 149, 150.
formation of, from its elements, 21.
cyanide, cyanoethylation of, 125.
rate of formation of, 65.
deuteride, formation of, 21.
deuterium selenide, 106.
fluoride, properties of solutions of, 109.
vapour, polymer structure in, 109.
iodide, decomposition of, 19.
formation and decomposition of, 52.
formation of, from its elements, 21.
peroxide in hydrogen-oxygen flames, 77.
in irradiated water, 28.
properties of, and its detn., 103, 104.
radiolysis of solutions of, 30.
Hydrogen selenide, photo-oxidation of, 106.
sulphide, decomposition of, by radiations, 19.
effect of, on acetaldehyde decomposition of, 54.
oxidation of, 77.
sulphides, 105.
Hydrogen-fluorine torch, 109.
Hydrogenolysis of organic sulphur compounds, 198.
Hydroxyl radical, 159.
detn. of, by absorption spectra, 76.
generation of, in water, 29.
identification of, 16.
Hydroxylamine, detn. of, coulometrically, 336.
from ammonia oxidation, 99.
Hydroxylation, 135.
Hypersensitivity in tuberculosis, 293.
Hypertension, amino-acids in, 278.
detection of, 279.
Hypochlorites, preparation of, 110.
Hyponitric acid, salts, 100.
Hypophosphorous acid, preparation of, 101.
Hypoxanthine, 250.
Ice, action of α -rays on, 23.
Indates, preparation of, 94.
Indicator equilibrium displacement, 42.
Indicators for titration in acetic acid, 335.
isotopic, 84.
Indium, organic precipitant for, 94.
Indium halides, hydrolysis of, 94.
trihalides, solubility of, in inorganic solvents, 94.
hydroxide, precipitation of, 94.
sulphates, equilibrium of formation of, 94.
Inorganic compounds, decomposition of, by radiations, 19.
nomenclature, 82.
salts, separation of, by chromatography, 283.
Inositol, as growth and nutritional factor, 313.
Insecticides, fluoroaminophosphine oxides as, 139.
Insulating materials, spark technique in analysis of, 325.
Insulin, amino-acids of, 286, 287.
chemistry of, 283.
chromatography with, 277.
digestion of, with chymotrypsin, 290.
effect of detergents on, 284.
heat precipitation of, 285.
mol. wt. of, 284.
peptides in, 279.
reaction of, with formaldehyde, 291.
with keten, 290.
structure of, 288.
sulphate, 291.
Iodic acid, 111.
Iodide-coating of reaction vessels, 69.
Iodine, radioactive, 110.

- Iodine solutions, colour of, 110.
 standard, 332.
 Iodin in as bacterial growth inhibitor, 311.
 Ion pairs, mean energy to create, 12.
 Ions, negative, 14.
 positive, identification and stability of, 13.
 Ionisation potential data, 14.
 Iron, detn. of, in sea water, 343.
 electrolytic, as volumetric standard, 333.
 hydrides, 111, 112.
 oxidation of, 112.
 phosphates, 112.
 Isopolytungstates, absorption spectra of, 109.
 Isotopes, abundance rules for, 83.
 use of, as tracers in biosynthesis, 239.
 Jasmone, 163.
 Keten, reaction of, with insulin, 290.
 β -Keto-esters, synthesis of, 129.
 Ketones, aliphatic, reaction of, with acetyl peroxide, 141.
 reduction of, 123.
 heating of, with ammonium formate, 129.
 reduction of, 122.
 synthesis of, from benzyl acylmalonates, 129.
 Kieselguhr chromatograms, 270.
 Kinetics, chemical, 51.
 Krypton, isotope abundance of, 85.
 β -Lactam, synthesis of, 131.
Lactobacillus casei fermentation factor, 229.
 Lake water. *See under* Water.
 Lanthanons, 115.
 Lanthanon chlorides, 115.
 Lauric acid, potassium salt, density of solutions of, 51.
 Lead, reaction of, with sulphur dioxide, 98.
 Lead oxide, oxidation of, 97.
 pentafluoroaluminate (-2), 98.
 Leprosy, chaulmoogra oil treatment of, 314.
 treatment of, with sulphetrone, 306.
 Leucine, turnover of, in liver peptide, 276.
n- and *iso*-Leucine, detn. of, 280.
 Licheniformin, inhibition of tuberculosis by, 309.
 Limonene, reaction of, with iodoform and acetyl peroxide, 151.
 Lipoids, tubercle, biological properties of, 297.
 Lipositol, inhibition of streptomycin activity by, 309, 313.
 Lithium, Grignard reactions with, 86.
 Lithium aluminium hydride, preparation of, and its use in synthesis, 122.
 carbonate, hydrolysis of, 86.
 trichlorocobaltate, 112.
 Liver, co-enzyme A in, 262.
 Liver extracts, acetylation mechanism in, 262.
 fractions from, detected with *Lactobacillus lactis*, 232.
 spectrographic analysis of, 325.
 Lysine, conversion of, into α -amino-adipic acid in the body, 276.
 Macromolecules, partition chromatography of, 271.
 Magnesium carbides, formation of, 89.
 chloride, anhydrous, preparation of, 89.
 dichromate, preparation of, 89.
 hydroxide, precipitation of, by ammonia, 99.
 sulphide, formation of, 89.
 Maleic acid, esters, addition reactions of, in presence of benzoyl peroxide, 154.
 reaction of, with diazonium salts, 155.
 Malonic acid, amino-, formyl derivative, ethyl ester, as intermediate in amino-acid synthesis, 131.
 Manganese, detn. of, in sea water, 343.
 Manganese carbide, hydrolysis of, with hydrogen chloride and with water, 111.
 dioxide, compound of, with sodium oxide, 111.
 Manganese(II) hydroxide, oxidation of, 112.
 "Maninositose", 313.
 Manööl, configuration of, 186.
 Manööl oxide, configuration of, 186.
 Mercaptals, hydrogenolysis of, 201.
 Mercury, detn. of, in sea water, 344.
 isotopes, reflux still for concentrating, 91.
 Mercury(I) perchlorate for ferric iron detn., 332.
 Mercury(II) bromide and chloride, hydrolysis of, 91.
 chlorite, red, preparation of, 91.
 ethylenediamine complexes, 92.
 nitrate in nitric acid, oxynitration with, 137.
 sulphides, 91.
 Mesaconic acid, reaction of, with diazonium salts, 155.
 Metal amines, salts, preparation of, 85.
 surfaces, properties and state of, 84.
 Metals, oxides formed on surface of, 103.
 properties of, in liquid ammonia solution, 99.
 separation of, by chromatography, 283.
 spectrographic analysis of, 324.
 Metallic chlorides, anhydrous, preparation of, from the hydrated salts, 85.
 complexes, stability of, 84.
 phenoxides, 85.
 Methacrylic acid, methyl ester, polymerisation of, 157, 158.
 Methane, bromination of, 64.
 mechanism of oxidation of, 18.
 Methane, trichlorobromo-, addition reactions of, 151, 152.
 halogen derivatives, addition reactions of, with ethylenic compounds, 150.

- Methionine, detn. of, 280.
 sulphone, detection of, 278.
 sulphoxide, detection of, 279.
 synthesis of, 131.
 Methoxymethylchanodihydrostrychnone, 202.
p-Methoxyphenylacetic acid, preparation of, 128.
p-Methoxy-*n*-propylbenzene, reaction of, with acetyl peroxide, 141.
 Methyl alcohol as methylating agent, 135.
 bromide, bromination of, 64.
 n-butyl ether, decomposition of, 59.
 cyanide, hydroxy-, 126.
 ether as methylating agent, 135.
 ethyl ketone, decomposition of, 58.
 radical, selective action of, 141.
 Methyladrenaline, separation of, 282.
 Methylarsinatomolybdates, 108.
 Methylation with diazomethane, 135.
 3-Methyl-2-butyleyclopent-2-en-5-olone, synthesis of, 168.
 Methyl dioctylamine, 132.
 α -Methylenic groups, reaction of, with *N*-bromosuccinimide, 156.
 "9-Methylfolic acid", 233.
 2-Methylfuran, 133.
 Methylhistidine in urine, 279.
O-Methylhydroxylamine, reaction of, with Grignard reagents, 130.
 2-Methyl-1:4-naphthaquinone as growth factor for John's bacillus, 311.
 γ -(2-Methylnaphtha-3-quinonyl)butyric acid, 142.
 β -(2-Methylnaphtha-3-quinonyl)propionic acid, 142.
 2-Methyl- Δ^2 -oxazoline, 219.
 Methylcyclopentane, decomposition of, 60.
O-Methylpodocarpic acid, reduction of, 182.
O-Methylpodocarpinol, 182.
 9-Methylpteridine, 2-amino-6-hydroxy-, 237.
 2:6-dihydroxy-, 236.
 2-Methylthioadenines, 9-substituted, hydrogenolysis of, 205.
 β -Methylthiopropaldehyde from acetaldehyde, 130.
 9-Methylxanthopterin, 237.
 8-Methylisoxanthopterin, 237.
 Micelles, laminar and spherical, 46.
 "Micro-icebergs," 27.
 Micro-organisms, carbohydrate metabolism of, 281.
 Microphotometers, 319.
 Minerals, spectrographic analysis of, 325.
 Miropinic acids, 180.
 Moissan, life of, 109.
 Molecules, small, function of, in biosynthesis, 239.
 Molybdates, 108.
 Molybdenum-blue, formula for, 108.
 Molybdic acid, reaction of, in solution with copper, iron, or tin salts in presence of thiocyanates, 108.
 solutions of, 108.
 Monazite, chlorination of, 115.
 Monochromators, 326.
 Monoterpenes, 162.
 Muscle adenylic acid, synthesis of, 138.
Mycobacterium leprae. See Bacilli, leprosy.
Mycobacterium paratuberculosis. See Bacilli, John's.
Mycobacterium phlei. See Bacilli, timothy-grass.
Mycobacterium tuberculosis. See Bacilli, tubercle.
 Mycolic acid, 297.
 Myelinic figures, 49.
 Naphthalene, chloromethylation of, 136.
 methylation of, 136.
 nitration of, 137.
 solubility of, in acetone-water and in paraffin-chain salts, 40.
 Naphthalene, chloro-, chloromethylation of, 136.
 Naphthalene-1-acetic acid, preparation of, 128.
 Naphthaquinones as growth factors for bacilli, 311.
 β -Naphthol, sulphomethylation of, 137.
 α -Naphtholbenzoin as indicator in titrations in acetic acid, 335.
 α - and β -Naphthoyl peroxides, reaction of, on carbon tetrachloride, 141.
 Naphthylhydroxylamine, nitroso-, thallium(III) complexes of, 94.
 4- β -Naphthylmorpholine, 211.
 Nativinsulin, 284.
Nematospora gossypii, inositol as growth factor for, 313.
 Neodymium tetracyanonickelate, 114.
 Neon isotopes, separation of, 85.
 Neophyl radical, 148.
 Neptunium, properties of, 117.
 Neutrons, ionisation and polymerisation induced by, 8.
 Nickel carbonyl, structure of, 114.
 Raney, as catalyst, 198, 199.
 for hydrogenation, 124.
 hydride, 112.
 Nickel(II) hydroxide, oxidation of, 112.
 Nicotine, detn. of, volumetrically, 335.
 Ninhydrin, as reagent for paper chromatograms, 274.
 Niobates, 103.
 Niobium nitrides, 103.
 Niobium pentoxide, heating of, in hydrogen, 103.
 Nisin, chemotherapy with, 309.
 Nitrates, detn. of, in sea water, 342.
 Nitration, 137.
 Nitric oxide. See Dinitrogen dioxide.
 Nitrilotriacetic acid, metallic complexes with, 84.
 Nitritopentamminocobalt(+2) nitrate, 113.
 Nitro-compounds, aromatic, methylating agent for, 158.
 Nitrogen, active, action of, on hydrazoic acid, 99.

- Nitrogen, oxidation of, in explosive mixtures, 65.
 preparation of, 99.
 Nitrogen tribromide, attempts to produce, 101.
 trichloride, m.p. of, 101.
 fluorides, 100.
 hydrides and oxides, decomposition of, by radiations, 19.
 triiodide, impact detonation of, 19.
 organic compounds, detn. of, in sea water, 342.
 oxides, reactions of, with ammonia, 99.
 See also under Dinitrogen.
 Nitrosation, 137.
 Nitrosoacetylaminines as polymerisation catalysts, 157.
 Nitrosyl compounds, 100.
 Nitrous oxide. *See* Dinitrogen monoxide.
 Nitryl chloride, action of hydrogen peroxide on, 100.
 Nomenclature, 82.
 Noradrenaline, separation of, 282.
 Nucleotides, detection of, in chromatograms, 275.
 separation of, by ultra-violet absorption chromatography, 281.
 Octadecylpyridinium iodate, conductivity in solutions of, 39.
*cyclo*Octatetraene, structure of, 187.
 Oct-1-ene, reaction of, with ethyl bromoacetate, 153.
 with methyl dichloroacetate or trichloroacetyl chloride, 152.
 with phosphorus trichloride and with trichlorosilane, 153.
 with sulphuryl chloride, 157.
 Oils, dissolving of, in soap solutions, 47.
 Olefins, conversion of, into primary alcohols, 134.
 platinum complexes with, 114.
 Oleic acid, conversion of, into 9:10-dihydroxystearic acid, 135.
 ethanolamine salt, adsorption of water vapour by benzene solutions of, 43.
 sodium salt, consolution of mixed liquids by, 43.
 solubility of hexane in, 40.
 Olivenite, 86.
 Organic compounds, action of radiations on, 22.
 Organisms, marine, copper content of, 344.
 Orotic acid as precursor of pyrimidines, 246.
 Oxalato-calcium chloride, 90.
 Oxalato-indates, 94.
 Oxalic acid, silver salt, decomposition of, 88.
 Oxaloacetic acid, enzymic decomposition of, 265.
 Oxaloacetic carboxylase, 265.
 Oxalosuccinic carboxylase, 266.
 Oxidising agents, irradiation of solutions of, 24.
 "Oxo" reaction, 134.
 Oxycodochicine, 194.
 Oxygen, effect of, on acetaldehyde decomposition, 53.
 explosive combination of, with hydrogen, 104.
 ozone formation from, 19.
 reaction of, with hydrogen, 67, 69.
 with hydrogen sulphide, 78.
 with nitrogen, 65.
 structure of, 104.
 Oxynitration, 137.
 Ozone, structure of, 103.
 Ozoniser, 103.
 Oysters, copper content of, 344.
 Pantothenic acid, role of, in pyruvic metabolism, 262.
 Pantoyltaurine, bacteriostatic activity of, 312.
 Paper chromatograms, separations with, 278.
 Papyrography, 268.
 Paraffins, dehydrogenation of, by rays, 22.
 Paraffin-chain salts, 33.
 density of, 50.
 equilibria of, with alcohols or amines, oil, and water, 43.
 solubility in, 40.
 Paraffin oil, consolution of water and, by sodium oleate, 43.
 Parsley root, oxaloacetic carboxylase in, 266.
 Partition coefficients, factors influencing, 269.
 Penicillin, chromatography with, 277.
 detection of, in chromatograms, 275.
 separation of, 282.
Penicillium stipitatum, 188.
*cyclo*Pentadiene, reaction of, with *cis*- and *trans*-1:2-dicyanoethylene, 127.
*cyclo*Pentadiene, *hexachloro*-, 96.
 Pentagermanic acid, 97.
 Pentamethylene dibromide, conversion of, into cadaverine, 130.
*cyclo*Pentane, decomposition of, 60.
 Pent-2-ene, hexaldehydes from, 134.
*cyclo*Pentene, decomposition of, 60.
 Pentenynol, 133.
 Peptide bond synthesis, 242.
 Peptides, detection of, in insulin, wool, and urine, 279.
 separation of, 278.
 Performic acid, hydroxylation by, 135.
 Periodic acid, and its salts, 111.
 Periodic tables, 83.
 Peroxides, reactions of, 140.
 Peroxyborates, 104.
 Peroxycarbonates, 104.
 Peroxymolybdates, 104.
 Peroxynitric acid, 100.
 Peroxy-salts, 104.
 Peroxytungstates, 104.
 Peroxyvanadates, 104.
 Per-rhenates, 111.
 Peyronet's salt, 114.

- Phagocytes, mono- and poly-morpho-nuclear, 294.
- Phenanthrene, hydroxylation of, 198.
- Phenol, chloromethylation of, 136.
- Phenols, bactericidal properties of, in paraffin-chain salt solutions, 42.
- equilibria of, with soaps and water, 43.
- reaction of, with ethynyl ketones, 134.
- Phenols, *o*-nitro-, preparation and properties of, 137.
- p*-nitroso-, 137.
- Phenyl isocyanate, reaction of, with diazomethane, 131.
- radical, 155.
- Phenylacetic acid, reduction of, to 2-phenylethanol, 123.
- N*-Phenylacetyl-L-(+)-alanyl-D(-)-valine, 200.
- Phenylalanine, detn. of, 280.
- D,L*-Phenylalanine, 131.
- Phenylalanyl-valyl-aspartyl-glutamic acid, 289.
- Phenylamino-acids, *d*initro-, separation of, 277.
- Phenylazo- β -naphthylamine, solubility of, in soap solutions, 42.
- Phenyl benzyl sulphone, vinyl cyanide addition to, 124.
- β -Phenylcysteine, preparation of, 216.
- Phenyldimorpholinomethane, 211.
- Phenylethynyl bromide, reaction of, with Grignard reagents in presence of cobalt chloride, 161.
- Phenylglyoxylic acid, reduction of, to phenylethylene glycol, 123.
- 1-Phenylpropane, 3-chloro-, reaction of, with Grignard reagents in presence of cobalt chloride, 160.
- Phenylpyridines, 158.
- 5-Phenylpyrimidine, 4-amino-, 127.
- Phenyl 2-thienyl ketone from thiophen, 129.
- Phenylthioacetamidoacetic acid, methyl ester, 207.
- β -Phenylisovaleraldehyde, reaction of, with *tert*.-butyl peroxide, 148.
- Phenylvinylmethyl radical, 161.
- properties of, 142.
- Phosphates, absorption spectra of, 109.
- detn. of, in sea water, 338.
- Phosphatides, brain, inositol in, 313.
- from tubercle bacilli, 296.
- Phosphine. *See* Phosphorus trihydride.
- Phosphomolybdic acid, 109.
- Phosphoric acids, 101.
- Phosphoroclastic reaction, 265.
- Phosphorous acid derivatives, platinum complexes with, 114.
- Phosphorus, colourless and red, 101.
- nitrogen compounds of, 102.
- Phosphorus trichloride, addition reactions of, in presence of peroxides, 153.
- chlorides, addition of, to organic compounds, 138.
- halides, oxy- and sulpho-halides, 102.
- Phosphorus trihydride, oxidation of, with aqueous iodine suspensions, 101.
- platinum complexes with, 114.
- organic compounds, detn. of, in sea water, 339.
- reactions of, 138.
- oxydichlorofluoride, reactions of, with alcohols, amines, phenols, and thiols, 138.
- Phosphorylation, 138.
- Phosphotungstates, spectra and stability of, 109.
- Phosphotungstic acid, 109.
- Phospho-12-vanadate ion, degradation of, 103.
- Photocells, multiplier, 323.
- Photo-electron multipliers, 323.
- Photographic emulsions, effect of ultra-violet light on, 321.
- plates, calibration of, 320.
- Photometer, flame, 326.
- Photometry, flame, 326.
- Photons, high-energy, absorption of, 11.
- Phthalic acid, dimethyl ester, solubility of, in paraffin-chain salts, 41.
- Phthiocol, antigens from, 302.
- as growth factor for John's bacillus, 311.
- Phthiolic acid, 297.
- Pigments, petal-extract, detection of, in chromatograms, 274.
- Pimanthrene, 178.
- Pimaric acid, permanganate oxidation of, 182.
- structure of, 179.
- Pinus palustris*, analysis of oleoresin from, 174.
- Plankton, detn. of phosphorus in, 340.
- Plants, spectrographic analysis of, 324.
- Platinum compounds, complex, 114.
- pure, preparation of, 114.
- Plutonium, properties of, 117.
- Podocarpic acid, structure of, 180.
- Podocarpinol, oestrogenic activity of, 182.
- Podocarpus ferrugineus* resin, 180.
- Pollen, amino-acids in, 278.
- Polonium isotope in Roumanian minerals, 107.
- α -rays from, 6, 16.
- Polyethyleneimine, 217.
- Polygalitol, synthesis of, 203.
- Polymerisation, catalysts for, 157.
- mechanism of, 139.
- radiochemical, 22.
- Polymixin, chromatography of, 279.
- detection of, in chromatograms, 275.
- Porphyryns, biosynthesis of, 253.
- detection of, in chromatograms, 274.
- formation of, from pyrroles, 257.
- Positron-electron pairs, 11.
- Potassium, comparison of, with sodium, 86.
- detn. of, 327, 329, 330.
- Potassium bismuthate, 103.

- Potassium *tetraborate*, reaction vessels coated with, 69.
 carbonate, hydrolysis of, 86.
 chloride, reaction vessels coated with, 68.
 hydride, dissociation pressure of, 86.
 iodide as volumetric standard, 332.
 iodoplatinate as reagent for sulphur-containing amino-acids, 274.
 paraperiodate as volumetric standard, 330.
 rhenium iodate, 111.
 Potatoes, amino-acids in, 278.
 Proabietic acid, 174.
 Prodigiosin, 258.
 Proline, biosynthesis of, 243.
 R_F value for, 273.
 Promethium, 83.
 Promin, antibacterial action of, on tubercle bacilli, 305.
 chemotherapy with, 293.
 Promizole, chemotherapy with, in tuberculosis, 306.
 Prontosil rubrum, chemotherapy with, 305.
 Propaldehyde, decomposition of, 58.
*cyclo*Propane, isomerisation of, to propylene, 57.
*cyclo*Propenone, 133.
 Propionic acid, *tert.*-butyl ester, decomposition of, 60.
 Propionic acid, α -*dichloro*-, preparation of, 125.
 Propyl chlorocarbonate, decomposition of, 60.
*iso*Propylbenzene, reaction of, with acetyl peroxide, 141.
 with Grignard reagents in presence of cobalt chloride, 161.
 Propylene as retarder of reactions, 58.
 effect of, on reaction rate, 52.
 hydrogen chloride addition to, 150.
 vapour, solvents for, 42.
n-Propyltrichlorosilane, chlorination of, 156.
 Protamine-zinc-insulin, mol. wt. of, 284.
Proteus morganii, co-enzyme A in, 262.
 pyruvic metabolism by, 262.
 Protons, spectra of light emitted from beams of, 16.
 Protoporpyrin methyl ester, 255.
 Pteridine, 2-mercapto-, 234.
 6 : 8 : 9-*tri*hydroxy-2-mercapto-, 234.
 Pteridines, preparation of, 233.
 refluxed, 228.
 synthesis of, from diaminopyrimidines and sugars, 234.
 Pteridine-8-aldehyde, 2-amino-6-hydroxy-, 229.
 Pteridinecarboxylic acids, aminohydroxy-, 234.
 Pteridine-8-carboxylic acid, 2-amino-6-hydroxy-, 230.
 Pterins, 226.
 detection of, in chromatograms, 274.
 separation of, 282.
- N*-[γ -(γ' -Pteroamido- γ' -carboxybutyramido)- γ -carboxybutyryl]glutamic acid, 231.
N-(α -Pteroamido- γ -carboxybutyryl)-glutamic acid, 230.
N-(γ -Pteroamido- γ -carboxybutyryl)-glutamic acid, 231.
 Pteric acid, ethyl ester, preparation of, 228.
 synthesis of, 228.
 Pteroylaspartic acid, antagonist to vitamin-Bc, 233.
 Pteroylglutamic acid. *See* Vitamin-Bc.
 Pteroylglutamic acid, 6-amino-, antagonist to vitamin-Bc, 233.
 Pteroyl-L-glutamic acid, 230.
 Pteroylglutamylidiglutamic acid, 230.
 Puberulic acid, 188.
 Puget Sound, detn. of nitrogen in water of, 343.
 Purines, biosynthesis and metabolism of, 245.
 detection of, in chromatograms, 275.
 synthesis of, 215.
 Purpurogallin, 189.
 methyl ether, 190.
 oxidation of, in air in presence of alkali, 190.
 Purpurogallincarboxylic acid, 190.
 Purpurogallone, 189.
*iso*Purpurogallone, 189.
 Pyramidon, lanthanon complexes with, 115.
 Pyrethrins, and their derivatives, 164.
 formulæ of, 162.
 Pyrethrolone, 163, 169, 170.
 Pyrethrum flowers, insecticidal constituents of, 162.
 Pyridine-aldehydes, 214.
 Pyridinocopper(-2) perchlorate, dissociation pressures of, 88.
 Pyridinoheteropolymolybdates, 108.
 Pyridinoheteropolytungstates, 108.
 Pyrimidine, 5 : 6-*diamino*-4-hydroxy-, preparation of, 205.
 4 : 5-*diamino*-2-mercapto-, 234.
 Pyrimidines, synthesis of, 215, 245.
 Pyrimidines, 4 : 5-*diamino*-, pteridine synthesis from, 234.
 Pyrimidine-aldehydes, 214.
 Pyrogallol, oxidation product of, 189.
 Pyrophosphoric acid, hydration of, 102.
 Pyrroles, formation of porphyrins from, 257.
 Pyruvic acid, condensation of, with glycine, 256.
 metabolism of, by *Proteus morganii*, 262.
 reaction of, with phosphoric acid, 265.
 Pyruvoylglycine, properties of, 256.
- Quartz, synthetic, 96.
 Quinodiphenone, 196.
 Quinoline derivatives, synthesis of, with ethyleneiminyl-lithium, 219.
 Quinoline, 8-hydroxy-, thallium(III) complexes of, 94.

- Quinoline-aldehydes, 214.
 Quinones, alkylation of, with acyl peroxides, 142.
 Quinovose tetra-acetate, synthesis of, 204.
- Radiation, sources of, 6.
 Radiation chemistry, 5.
 Radicals, free, chemistry of, 139.
 formation of, by means of rays, 159.
 identification of, 16.
 Radical-addition reactions, 149.
 Radical-addition rule, 149.
 Radical transfer in biosynthesis, 240.
 Radiochemical reactions, addition, 21.
 indirect, kinetics of, 31.
 mechanism of, 5.
 Radio-elements, α -rays from, 6.
 Radio-isotopes, use of, in partition chromatography, 275.
 Radish seed, sulphoraphen from, 201.
 Radium, γ -rays from, 8.
 Radon and its decay products, 6.
 "seeds," 7.
 Rapanone, 142.
Raphanus sativa var. *alba*, 201.
 Rate constant, first-order, calculation of, 62.
 Rays, action of, on water, 23.
 cathode, 7.
 ionising, 5.
 spectra of, 16.
 positive, 6.
 α -Rays, dose rate for, 9.
 sources of, 6.
 β -Rays, dose rate for, 9.
 sources of, 7.
 γ -Rays, absorption of, 12.
 dose rate for, 9.
 effect of, on water, 18.
 sources of, 7, 8.
 X-Rays, action of, on water and solutions, 25.
 dose rate for, 9.
 inactivation of biologically active substances by, 31.
 sources of, 7, 8.
- Reactions, addition, 149.
 branching-chain, 67.
 chain, intermediates formed in, 80.
 kinetics of, 64.
 first-order, 54.
 homolytic, 139.
 induced by ionising radiations, 5.
 second-order, 52.
 third-order, 54.
 unimolecular, theory of, 61.
 Reaction vessels, coated, 68.
 Recombination reactions, 27.
 Reducing agents, irradiation of solutions of, 24.
 Reduction, 122.
 Resins, copal, agathic acid from, 184.
 Resin acids, separation of, 174.
 Resorcinol, detn. of, volumetrically, 336.
 dioctyl ether sulphonate, interfacial tension of, against non-polar liquids, 36.
- Retention analysis, 280.
 Rhizopterin, 231.
apoRhizopterin, 231.
 Rhodamine, uses of, in syntheses, 215.
 Riboflavin and its phosphate, separation of, from tissues, 282.
 Ribonuclease, inactivation of, by X-rays, 31.
 Ribonucleosides, separation of, 282.
aldehydo-D-Ribose tetra-acetate, 204.
 Roccellic acid, chemotherapy with, in tuberculosis, 314.
 Rubber, thio-acid adducts of, 154.
 Rubeabietic acid, 175.
 Rubeanic acid. See Dithio-oxamide.
 Rubidium hydroxide, cell for preparation of, 86.
- S.L.R. factor, 231.
 Salicylaldehyde, cyanoethylation of, 125.
 Salicylic acid as volumetric standard, 330.
 chloromethylation of, 136.
 detn. of, volumetrically, 336.
 sodium salt, solubility of organic substances in, 41.
 Salicylic acid, *p*-amino-, bacteriostatic effect of, 306.
 Sampling, 319.
 Sapietic acid, structure of, 176.
l-Sapietic acid, 176.
 α - and γ -Sapinic acids, 175.
 Sea water. See Under Water.
 Sebacic acid, reduction of, to decano-1 : 2-diol, 123.
 Selenitomolybdates, 108.
 Selenium dioxide, structure and vapour pressure of, 107.
 Serine, biosynthesis of, 242.
 Selareol, configuration of, 186.
 Shiga polysaccharide, 281.
 Silica chromatograms, 269, 276.
 Silicates, detn. of, in sea water, 341.
 Silicomolybdic acid, 109.
 Silicon, comparison of, with carbon, 96.
 Silicon tetrachloride, synthesis and hydrolysis of, 97.
 chlorides, plastic, 97.
 compounds, chlorination of, 156.
 tetrafluoride, absorption of, by acids, and its hydrolysis by water, 97.
 fluoroisocyanates, 97.
 Silicotungstic acid, 109.
 Silver acetylides, 88.
 chromates, 88.
 cyanide, complex nature of, 87.
 hydroxide as volumetric standard, 331.
 oxides, active, preparation of, 88.
- Soaps, effect of aggregation on properties of, 50.
 equilibria of, with phenols and water, 43.
 X-ray diffraction patterns of, 44.
 Soap curd suspensions, optical anisotropy in, 49.
 Soap-like substances, structure of solutions of, 33.

- Soap solutions, dissolving oils in, 47.
 solvent power of, 42.
 structure of, 33.
- Sodium, comparison of, with potassium, 86.
 detn. of, 329, 330.
- Sodium acetylide, reaction of, with epichlorohydrin in liquid ammonia, 133.
 azide with iodine as reagent for sulphur-containing amino-acids, 274.
 benzylpenicillin, products from, heated with Raney nickel, 200.
 bismuthate, 103.
 bismuthide, 103.
 carbonate, anhydrous, preparation of, 331.
 hydrolysis of, 86.
 chlorite as volumetric standard, 332.
 hydride, reduction with, 123.
 hypochlorite solutions as volumetric standard, 332.
 hyponitrite, preparation and properties of, 100.
 manganates, 111.
 molybdate, solutions of, 108.
 dioxide, 86.
 phosphates, review, 101.
 thiosulphate solutions, stabilisation of, 331.
- Soils, spectrographic analysis of, 324.
- Solubilisation, 40.
- Solubility in paraffin-chain salt solutions, 40.
- Solutes, radiochemical transformation of, 29.
- Solutions, concentrated, organisation in, 44.
- Solvents, non-aqueous, titration in, 334.
- Soot, action of hydrogen on, 95.
- Spectra, direct measurement of line intensities in, 323.
 ultra-violet, for identification of atoms and radicals, 16.
- Spectrographs, direct-reading, 323.
- Spectrographic analysis, emission, 316.
- Standards for volumetric analysis, 330.
- Stannane from stannous chloride, 97.
- Stannous chloride, reduction of, by atomic hydrogen, 97.
- Starch chromatograms, 270.
- Starch, structure of, 281.
- Steam, rate of formation of, 72.
- Stearic acid, reduction of, to octadecanol, 123.
- Steel, spectrographic analysis of, 326.
- Stercobilin, 259.
- Stibonium salts, synthesis of, 138.
- Stilboestrol, methylation of, with diazo-methane, 135.
- Stipitatic acid, 187, 188.
- Streptidine, 308.
 synthesis of, 215.
- Streptobiosamine, 308.
- Streptomycin, chemotherapy with, in tuberculosis, 307.
- Streptomycin, chromatographic separation of, 271.
 detection of, in chromatograms, 274.
 inhibition of activity of, by lipositol, 309, 313.
 separation of, 282.
 structure of, 202.
 treatment of tuberculosis with, 293.
- Streptomycin A and B, constitution of, 307.
- Strontium hexanitritocobaltate(—3), 90.
- Styrene, hydrotropaldehyde from, 134.
 polymerisation of, 7, 157.
- Succinic acid, preparation of, from hydrogen cyanide, 125.
- Succinimide, *N*-bromo-, reactions and uses of, 155, 156.
- Sugars, methylated, separation of, 277, 281.
 preparation of acyl derivatives of *aldehydo*- or *keto*-forms of, 213.
 pteridine syntheses from diamino-pyrimidines and, 234.
- Sugar alcohol 1 : 5-anhydrides, 203.
- Sulphamic acid as volumetric standard, 330.
 preparation of, 106.
- Sulphethrone, chemotherapy with, 293, 306.
- Sulphitomolybdates, 108.
- Sulphomethylation, 137.
- Sulphones, aromatic, vinyl cyanide addition to, 124.
- Sulphonyl chlorides, preparation of, 157.
- Sulphoraphen, constitution of, 201.
- Sulphur, deposition of, from solutions in sunlight, 105.
 equilibria of forms of, 104.
 reaction of, with hydrogen, 105.
 with ethylene, 105.
- Sulphur hexafluoride, preparation and properties of, 109.
 fluorides, 106.
 halides and nitrides, 105.
 organic compounds, reactions of, 198.
monoxide, 79.
 oxy-acids, 106.
 oxychlorides, 104.
- Sulphuric acid, removal of nitrogen from, 106.
 standardisation of, 336.
- Sulphuryl chloride as peroxide-catalysed chlorinating agent, 156.
- Surface-active agents, fluorophosphates as, 102.
- Taurine in blood, 279.
- Technetium, chemistry of, adsorbed on copper or rhenium sulphides, 111.
- Telluric acid, 107.
- Tellurites, 107.
- Tellurium, chemical properties of, 107.
- Temperature control in radiochemical reactions, 8.
- Terbium, at. wt. and isotopes of, 115.
- Tergitols, 35.

- Teropterin, 231.
 Terpenes, 162.
 Tetramminocopper(+2) nitrite, thermal decomposition of, 88.
 Tetra-arylphosphonium salts, 138.
 Tetracalcium aluminoferrate, 90.
n-Tetradecane sodium sulphate, equilibria of, in oil-water mixtures, 43.
 sodium sulphates, critical concentration in solutions of, 38.
 X-ray structure of, 44.
 Tetrafluoboric acid, formation of, 93.
 Tetrahydroabietic acid, hydroxy-, 178.
 Tetrahydrofuran, decomposition of, 60.
 Tetrahydronaphthalene, autoxidation of, catalytic, 155, 159.
 chloromethylation of, 136.
 Tetrahydropyrene, 173.
 Tetrahydropyrene, 167.
 Tetrahydropyrene, 167.
 Tetrahydrostipitadic acid 2:4-dinitro-phenylhydrazones, 188.
 Tetramethyl glucose, R_f value for, 273.
 Tetramethyltin, decomposition of, 60.
 Tetrasilane, preparation and properties of, 96.
 Thallium sulphide, 94.
 tetracyanonickelate, 114.
 Thallium(I) carbonate as volumetric standard, 331.
 ferrate(III), 94.
 sulphate, conversion of, into sulphide, 94.
 sulphonylates, 94.
 Thallium(III), inner complex salts of, 94.
 Thianaphthens, conversion of, into phenyl-ethanes, 206.
 Thiazoles, preparation of, from 2-mercaptothiazoles, 206.
 Thiazole-aldehydes, 214.
 Thioacylamido-acids, preparation of, 207.
 Thioacylation, 207.
 Thio-amides, preparation of, 207.
 reduction of, to amines, 207.
 Thiobenzamidoacetic acid, ethyl ester, 207.
 Thiobenzanilide, 208.
 Thiobenzhydrazide, 208.
 Thiobenzmorpholide, 211.
 Thiobenzophenone, trisulphide from, 201.
 Thiobenzoyl chloride, preparation and reaction of, with aniline, 208.
 Thio-compounds, addition reactions of with olefins, 154.
 Thiocyanates, detn. of, coulometrically, 336.
 solutions, standardisation and stability of, 332.
 Thiodiglycol, detn. of, 337.
 Thioformamides, preparation of, 207.
 Thiols, addition of, to olefinic compounds, 149.
 nickel complexes with, 114.
 Thiol-esters, hydrogenolysis of, 204.
 preparation of, 204.
 Thione group in thio-amides, 206.
 Thion-esters, 208.
 Thionyl chloride, purification of, 106.
 chlorofluoride and fluoride, 106.
 Thionylimine, 106.
 Thiophen, acylation of, 129.
 aminomethylation of, 136.
 2-Thiothiazolidone, preparation and synthetic uses of, 216.
 Thiourea, use of, in syntheses, 215.
 Thorium, analytical chemistry of, 116.
Thuja plicata, compounds from, 189.
 γ -Thujaplicin, 189.
 Thyronine, synthesis of, 214.
 Titanium, preparation, properties, and uses of, 98.
 Titanium hydride as catalyst in selective hydrogenation, 124.
 oxides, 98.
 Titanous chloride as volumetric standard, 332.
 Titration in non-aqueous solvents, 334.
 Tobacco, detn. of nicotine in, 335.
 Toluene, reaction of, with *tert*.-butyl peroxide, 147.
 unimolecular fission of, 61.
 Toluene- ω -sulphonamide, reaction of vinyl cyanide with, 124.
o-Tolylazo- β -naphthol, soaps as solvents for, 42.
Torulopsis utilis, biosynthesis by, 243.
 Triazens for polymerisation, 157.
 Trichloromethyl radical, 155.
 Trichlorosilane, reaction of, with *o*-1-ene, 153.
 Triethylenetetrammine, cobalt complexes with, 113.
 3:7:12-Triketocholanic acid, condensation of, with ethylenedithiol, 202.
 Trimethylacetic acid, reduction of, to neopentyl alcohol, 123.
 Trimethylaluminium, decomposition of, 60.
 1:2:3-Trimethylbutane, dissolved in potassium laurate, density of, 51.
 Trimethylcolehicinic acid, 191.
N-benzoyl derivative, oxidation of, 194.
 3:12:15-Trimethyldecanoic acid, 298.
 Trimethyloctylammonium octylsulphonate, conductivity in solutions of, 38.
 2:4:5-Trimethyloxazole from alanine, 131.
 3:13:19-Trimethyltricosanoic acid, 298.
 2:2':2''-Tripyridyl in sea water analysis, 344.
 Trisilane, thermal decomposition of, 96.
 Trisithioacetophenone, 211.
 Tropolone, 187.
 Tryptophan, bacterial breakdown of, 279.
 detection of, in chromatograms, 274.
 Tubercle bacilli. *See under* Bacilli.
 Tubercles, origin and fate of, 292.
 permeability of, 293.
 Tuberculin, growth substances in, 311.
 Tuberculo-carbohydrates, 298.
 Tuberculo-phosphatide, 297.

- Tuberculo-proteins, 299.
 Tuberculosis, acquired resistance against, 299.
 caseation in, 294.
 chemotherapy of, 292.
 index, 302.
 tests for, 303, 304.
 Tuberculo-stearic acid, 296.
 Tuberculo-therapeutic compounds, potential, 310.
 Tungstates, absorption spectra of, 109.
 Tungsten tetrachloride and oxychloride, 108.
 Tungstic acids, 108.
 Tungstic oxide, action of chlorine on, 110.
 Turkey-red oil as solvent for dyes, 42.
 Tyrosine, detection of, in chromatograms, 274.
 detn. of, 280.
 Unsaturated compounds, polymerisation of, under irradiation, 22.
 Uranium carbides, fluorides, nitrides, and oxides, 116.
 in minerals, 116.
 Uranium(IV) sulphate, 116.
 Uranyl nitrate, hydrolysis of, 117.
 Urea, 252.
 Uric acid, biosynthesis of, 240.
 breakdown of, by *Clostridium cylindro-sporum*, 252.
 degradation of, 247.
 oxidation of, 251.
 Uricase, 251.
 Urine, amino-acids in, 278.
 methylhistidine in, 279.
 peptides in, 279.
 Uroporphyrins, synthesis of, 258.
 Uro-xanic acid, 251.
 Usnic acid, activity of, against tubercle bacilli, 312.
 Vaccines against tuberculosis, 300.
 Valine, detn. of, 280.
 Vanadates, 103.
 Vanadium arsenides, 103.
 Vapours, pyrolysis of, 56.
 Vessels for hydrogen sulphide-oxygen reaction, 78.
 for radiochemical reactions, 8.
 reaction, coated, 68.
 Vinyl cyanide, cyanoethylation with, 124.
 polymerisation of, 30, 157.
 by rays, 159.
 preparation of, 126.
 Vinylacetylene, reduction of, catalytic, 124.
 Vinylation, 132.
 Viruses, amino-acids in, 278.
 Vitamin-B₆, antagonists to, 232.
 catalytic hydrogenation of, 229.
 diethyl ester, 228.
 synthesis of, 227.
 Vitamin-K-active substances, organisms synthesising, 311.
 Volumetric analysis, 330.
 apparatus for, 333.
 "W-6," 199.
 Water, action of rays on, 23.
 action of γ -rays on, 18.
 lake, detn. of dissolved nitrogen in, 342.
 molecules, ionisation and excitation of, 26, 27.
 radiolysis of, 27.
 sea, analysis of, 338.
 spectrographic analysis of, 324.
 structure of, 103.
 vapour, action of rays on, 23.
 adsorption of, by ethanolamine oleate in benzene solution, 43.
 Wetting agents, 34.
 Willgerodt-Kindler reaction, 210.
 Windows, reinforced, for use with accelerating machines, 7.
 Wool, amino-acids in, 278, 279.
 peptides in, 279.
 reaction of, with sulphuryl chloride, 157.
*iso*Xanthopterincarboxylic acid, 6-amino-, 234.
 Xenon, decomposition of ammonia by X-rays in, 21.
 isotope abundance of, 85.
 Yeast, acetic acid oxidation by, 263.
 acetyl-methylcarbinol formation by, 264.
 autolysis of, in presence of ammonium carbonate, 254.
 biosynthesis of proline and serine in, 243.
 Zinc, detn. of, in sea-water, 343.
 ferri- and ferro-cyanides, complex, 91.
 hydride, 122.
 pure, preparation of, 90.
 salts, 90, 91.
 tetracyanonickelate, 114.
 Zirconium hydride, 98.
 dioxide, transformation of, at high temperatures, 99.
 preparation, properties, and uses of, 98.
 separation of, from aluminium, 98.
 from hafnium, 98.
 telluride, 99.

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